REGRESSION OF FIBROADENOMA IN RESPONSE TO CENTCHROMAN THERAPY, A RANDOMIZED CONTROL TRIAL

A DISSERTATION SUBMITTED TO

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DEPARMENT OF GENERAL SURGERY

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CERTIFICATE

This is to certify that the dissertation titled "REGRESSION OF FIBROADENOMA IN RESPONSE TO CENTCHROMAN THERAPY, A RANDOMIZED CONTROL TRIAL" is the bonafide work done by Dr.SABARIMALAI P, Post graduate student (2013-2016) in the Department of general surgery, Government Stanley Medical College and Hospital, Chennai under my direct guidance and supervision, in partial fulfil of the regulations of The Tamil Nadu Dr. M.G.R Medical University, Chennai for the award of M.S,Degree (General Surgery) Branch-I, Examination to be held in April 2016.

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DECLARATION

I, Dr.SABARIMALAI P Solemnly declare that this dissertation titled "REGRESSION OF FIBROADENOMA IN RESPONSE TO CENTCHROMAN THERAPY, A RANDOMIZED CONTROL TRIAL" is the is a bonafide work done by me in the Department of General Surgery, Government Stanley Medical College and Hospital, Chennai under the guidance and supervision of my unit chief.

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LIST OF ABBREVIATIONS

FA- Fibroadenoma

USG-Ultrasonogram

FNAC- Fine Needle Aspiration Cytology

ANDI-Aberration In Normal Development And Involution

ER-Estrogen Receptor

ERE-Estrogen Receptor Elements

SERM-Selective Estrogen Receptor Modulator

FSH-Follicle Stimulating Hormone

LH-Luteinizing Hormone

CONTENTS

INTRODUCTION

INTRODUCTION

Fibroadenoma (FA) is the most common tumour of breast in young females (<30 yrs) and second most common breast tumour in females. It is a benign condition. FA is responsible for 15% palpable breast lump. It is clinically presents as painless breast lump in reproductive age groups. FA is very rare as new lump over the age of 40 -45 yrs.

Most of the FA cases are self diagnosed and consult surgeon in fear of breast cancer. For the patients with small FA (<3cm) ,below the 30 yrs of age without suspicious cytology, FA is very slow growing hence simple observation with reassurance is enough because 15 to 30 % FA regress completely by simple observation over 1 to 6 yrs follow-up.

AIMS AND OBJECTIVES

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The purpose of this study is to find **the REGRESSION OF FIBROADENOMA IN RESPONSE TO CENCHROMAN THERAPY (ORMELOXIFENE)** in person who is willing for observation instead of excisional biopsy (enucleation) between 18 -30 yrs old.

Study design: Randomized control trial

Material: 80 Patients

Study and follow-up period : 6 months

INCLUSION CRITERIA:

1. Diagnosed as FA under triple assesment
2. Age 18 to 30 year
3. Fibroadenoma of sonographic size 3 cm or <3 cm
4. Patient not willing for excision (fear of scar)

5.Willing for observation with signed informed

Consent

Exclusion criteria:

1. Patient above 30 yrs old

2. Size larger than 3 cm

3. Past history or family history of ca breast

4. PCOD

5.Liver disease, renal failure

6. Lactation

7.Pregnant and who desire to pregnant 8.Complex fibroadenoma

HISTORICAL ASPECTS

HISTORICAL ASPECTS

Galen	130-200AD	A greek physician mentioned about breast and used the word oncos for tumours.
	6th centuary	Acoustics, the science of study started
john moir	1620	Explained the breast is composed of small glands
Jacques	1880	piezoelectric effect discovered
	1890	It was established that ovaries controls female reproductive system through a hormone.
Sir Francis galton	1893	constructed a whistle producing ultra Sound
Salomon	1913	noticed small block spots in xray film of amputated breast
Paul langevin	1917	The first technological application of ultrasound was an attempt to detect submarines

Allen and Doisy	1923	doisy found alcoholic extract of ovaries was capable of producing estrus.
	1929	active principle of estrogen obtained in pure form
Dr. Ludwig	1940	Used ultrasonic energy as medical tool on the human body
Leborgne	1951	Published his discovery that microcalcification are found in 30% of ca breast.
EGAN et al	1980	Expressed " the radiographic signs are so non specific that all punctuate microcalcification require histologic evaluation"
Maimonides medical center	1981	The first FNAC biopsy in the united sates was done and Eliminated the needs for hospitalization for biopsy.
LE Hughes	1987	Coined ANDI first time.
	1990	Centchroman (Ormeloxifene)marketed for OCPand DUB
by Dhar A ,Srivastava,aims, dpt of general surgery.	2007	Role of centchroman in regression of mastalgia and fibroadenoma,Study done

MATERIALS AND METHODS

MATERIALS AND METHODS

Patients attending general surgery op with complaints of breast lump between 18 to 30 yrs of age will be taken detailed clinical history, clinical examination, ultrasonagram (USG) of both breast and fine needle aspiration (FNAC)/ core needle biopsy

Patients who are all diagnosed as fibroadenoma (FA) and willing for simple observation with reassurance at least for 6 months will be included in this study after getting informed consent with sign in both tamil and English language.

Willing patients after randomization included in study group and control group. Patients in study group will get Centchroman 30mg orally on alternative days and for control group patients only observation with simple assurance. Study group patients will be reviewed after 1 week to check tolerance and later follow-up at 4, 8, 12, and 24 weeks.

USG will be done at 0 days, 12 and 24 weeks for both groups to assess regression.

VOLUME OF FIBROADENOMA:

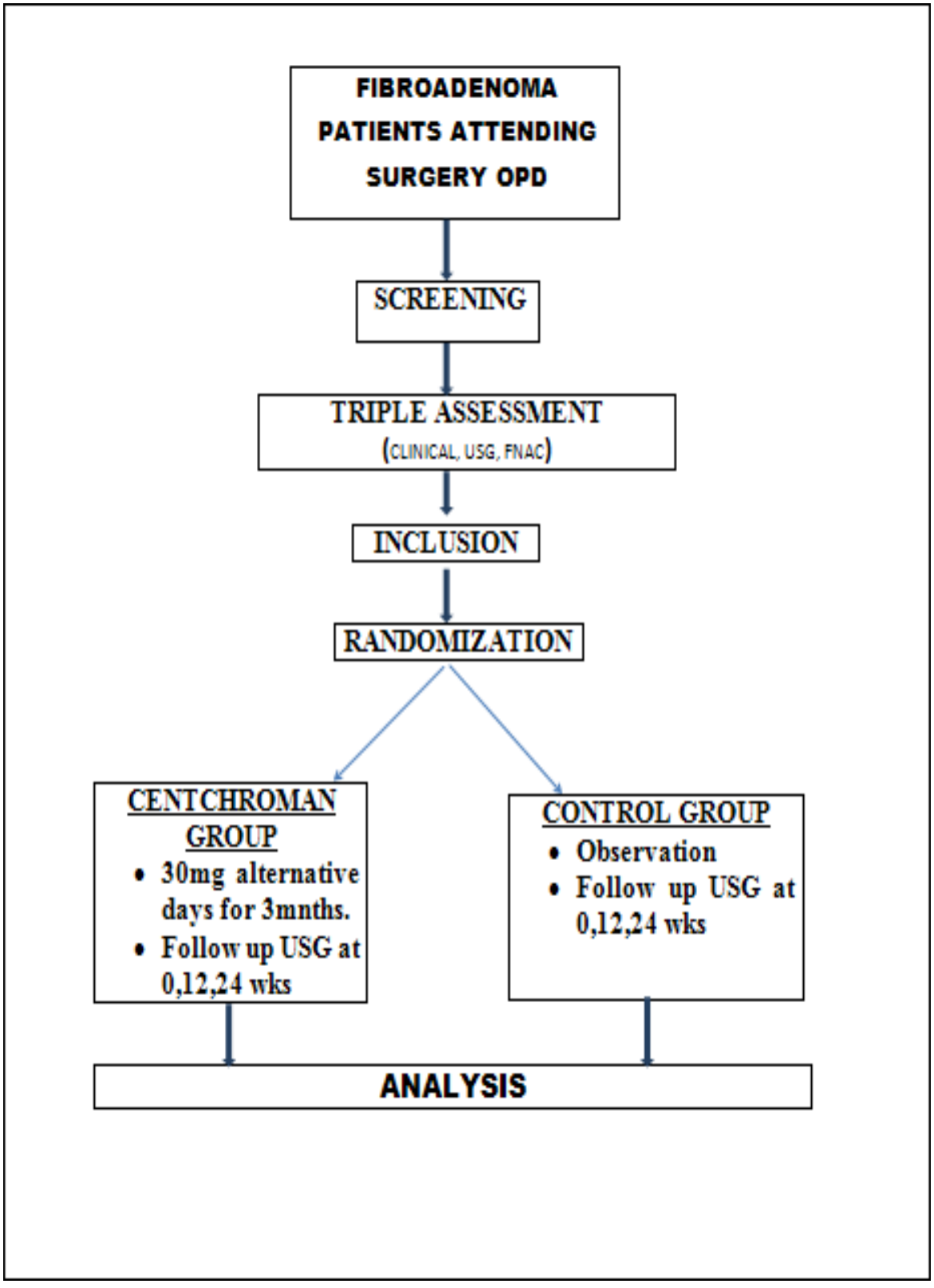
Size of FA was calculated by doing breast ultrasound using 7.5 – MHZ linear probe on “Siemens versa” ultra sound scanner. Volume in cubic centimetre is calculated by using following formula

SIZE – a × b × c × 0.52

a-largest dimension,

b- dimension at right angle to a.

c-a+b/2.


FIBROADENOMA PATIENTS ATTENDING SURGERY OPD
SCREENING
TRIPLE ASSESSMENT (CLINICAL, USG, FNAC)
INCLUSION
RANDOMIZATION
CENTCHROMAN GROUP
• 30mg alternative days for 3mnths.
• Follow up USG at 0,12,24 wks
CONTROL GROUP
• Observation
• Follow up USG at 0,12,24 wks
ANALYSIS

REVIEW OF LITERATURE

REVIEW OF LITERATURE

EPIDEMIOLOGY

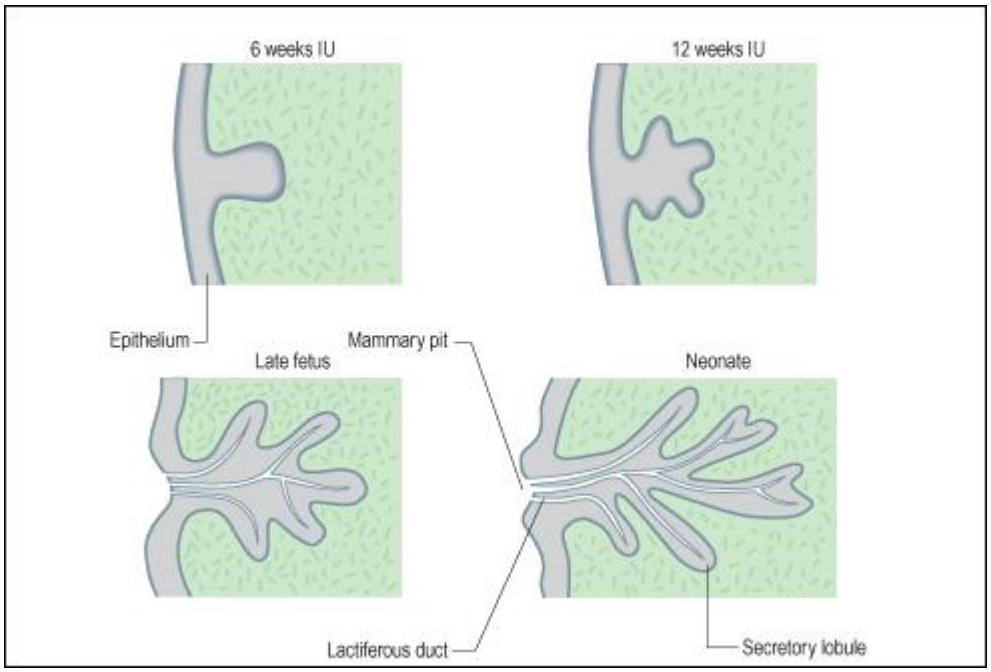
Benign breast diseases particularly fibroadenoma because of its high prevalence, fear of cancer and its impacts on quality of women life. It is the most common benign tumour of the breast below 30 yrs old females. It comes under Aberration in normal development and involution (ANDI). Incidence of fibroadenoam is 15 % of all palpable breast lumps. FA is bilateral in 20 % and multiple in 20 % of cases.

Fibroadenoma is common in blacks and negroes.Endocrine factors are involved in the etiology of fibroadenoma but their precise roles remains to be elucidated. There is no modifiable risk factor for fibroadenoma. Benign breast disorders has an incidence of 1.5/1000

total hospital admissions, 6.4/1000 of surgical admissions and 8.1/1000 of adult female admissions in india.

EMBRYOLOGY

The epithelial/ mesenchymal interactions will give rise to the glandular tissue of the breast, can be seen at first on 5th or 6th weeks when two ventral bands of ectoderm, the mammary ridges/milklines, extend from axilla to inguinal region. Invagination of thoracic bud occurs on 49th day and the remaining mammary lines involutes.

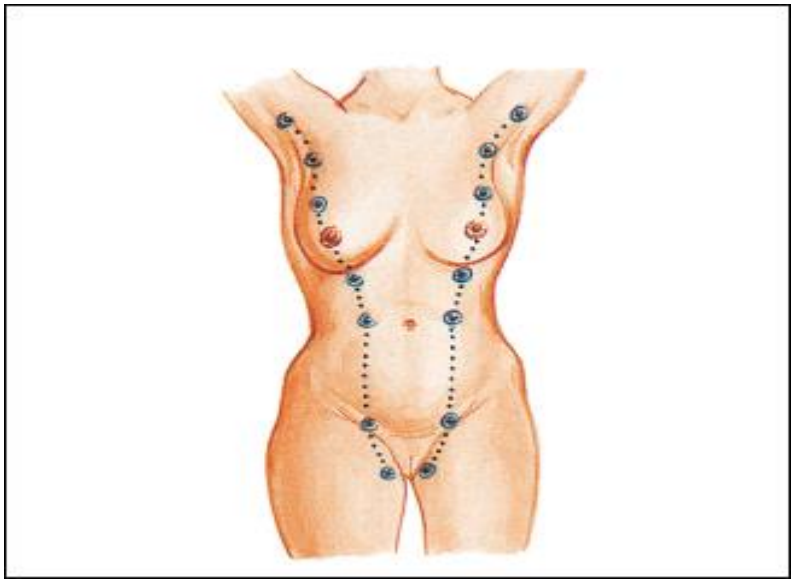


Thoracic ectodermal ingrowths branches into 15 to 20 solid buds which becomes the lactiferous ducts and their associated lobes of alveoli. They are surrounded by somatopleuric mesenchyme which forms the connective tissue, vasculature and fat which is invaded by the nerves. Proliferation, elongation and branching the alveoli are formed and the duct system becomes well defined. Nipple formation occurs on 56^{th} day and primitive duct develops on 84^{th} days with canalization occurring on 150^{th} day. The ducts become canalized during the last 2 months of gestational period. Small mammary pit developed by the epidermis at the point of original development of the mammary gland into which the lactiferous tubules open. Mesenchymal proliferation forms the nipple perinatally.

CONGENITAL INVERSION OF NIPPLE

It occurs in 3% of female population. Bilateral in 85% cases and unilateral in 15% cases. It may cause recurrent mastitis and difficulty

in breast feeding and has psychological implications but it can be corrected surgically.



ATHELIA -Congenital absence of nipple but this occurs commonly in accessory breast tissue

Polymastia- supernumerary breast

Polythelia- Supernumerary nipples which is more common in males.

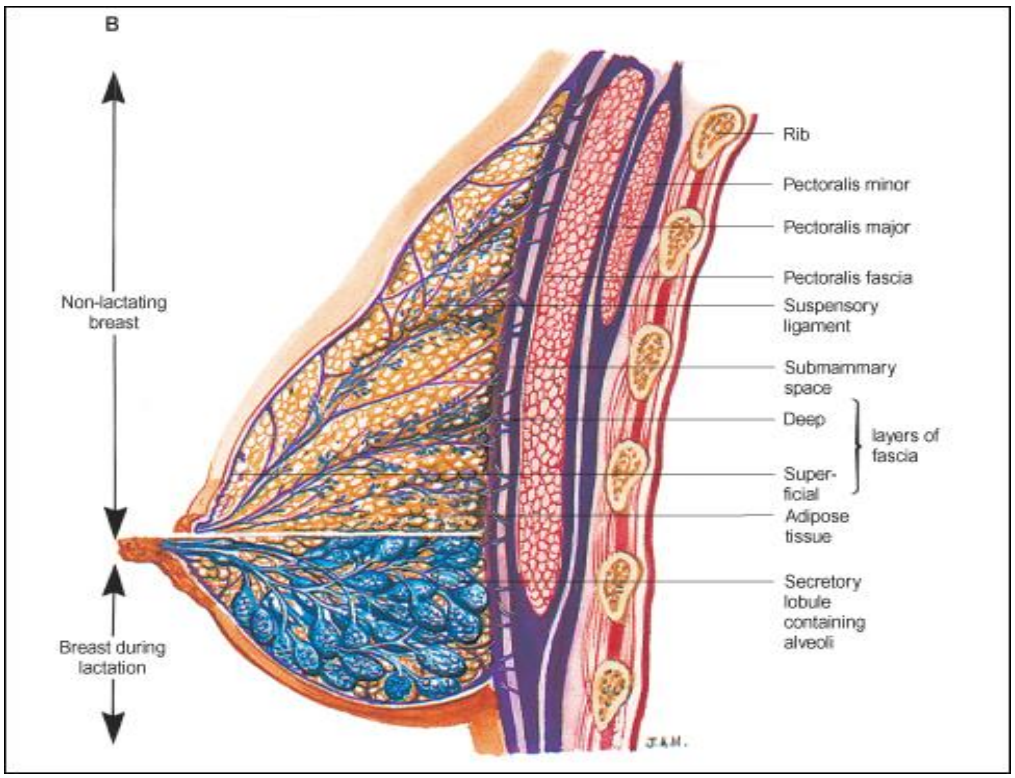
Amastia –Congenital absence of breast

Amazia-nipple development without breast tissue

BREAST ANATOMY

Breast is a modified sweat gland which vertically extends from 2nd to 6th rib in the MCL and horizontally from the side of sternum to mid axillary line and lies over pectoralis major, serratus anterior and external oblique muscles.

It forms secondary sexual character of females and it is the eource of nutrition for neonates. It also present males but in rudimentary form. Shape and size of the breast depends on the of the racial, genetic,dietary factors and the age, parity and menopausal status of the individual.



SKIN

Female breast is covered by modified thin skin of the anterior thoracic wall and bears fine hairs. Skin over the nipple and areola lacks hair and contains sweat and sebaceous glands which open directly . Oily secretion from this sebaceous gland form protective lubricant during lactation. Melanocytes are numerous in nipple and areola complex

Skin of the breast supplied by branches from the 1.anterior intercostals arteries 2.lateral thoracic artery, a branch of axillary artery 3.posterior intercostals arteries.

Venous drainage of nipple and areola forms circular venous plexus which drains into the veins accompanying corresponding arteries.

Lymphatics from the lateral side of breast skin drains into pectoral nodes ,lymphatics from skin near drains into parasternal nodes and there is anastamosis across the sternum and few from upper pectoral region drains into inferior deep cervical nodes.

SOFT TISSUE

Breast is composed of 15-20 lobes each of which consist of branching ducts and terminal lobules in a stroma. Stroma around the lobules is dense and fibrocollaagenous but intralobular connective tissue has a loose texture which

enables rapid expansion during pregnanacy. Adipose tissue in the interlobar stroma is responsible for increase in breast size during pregnanacy.

AXILLARY TAIL OF SPENCE:

It is a prolongation of the outer part of the mammary gland and reach upto the level of the 3rd rib in axilla through foramen of langer in the deep fascia which is in direct contact with the axillary lymphnodes.

Retromammary bursa is located between the deep layer of superficial fascia and pectoral fascia.

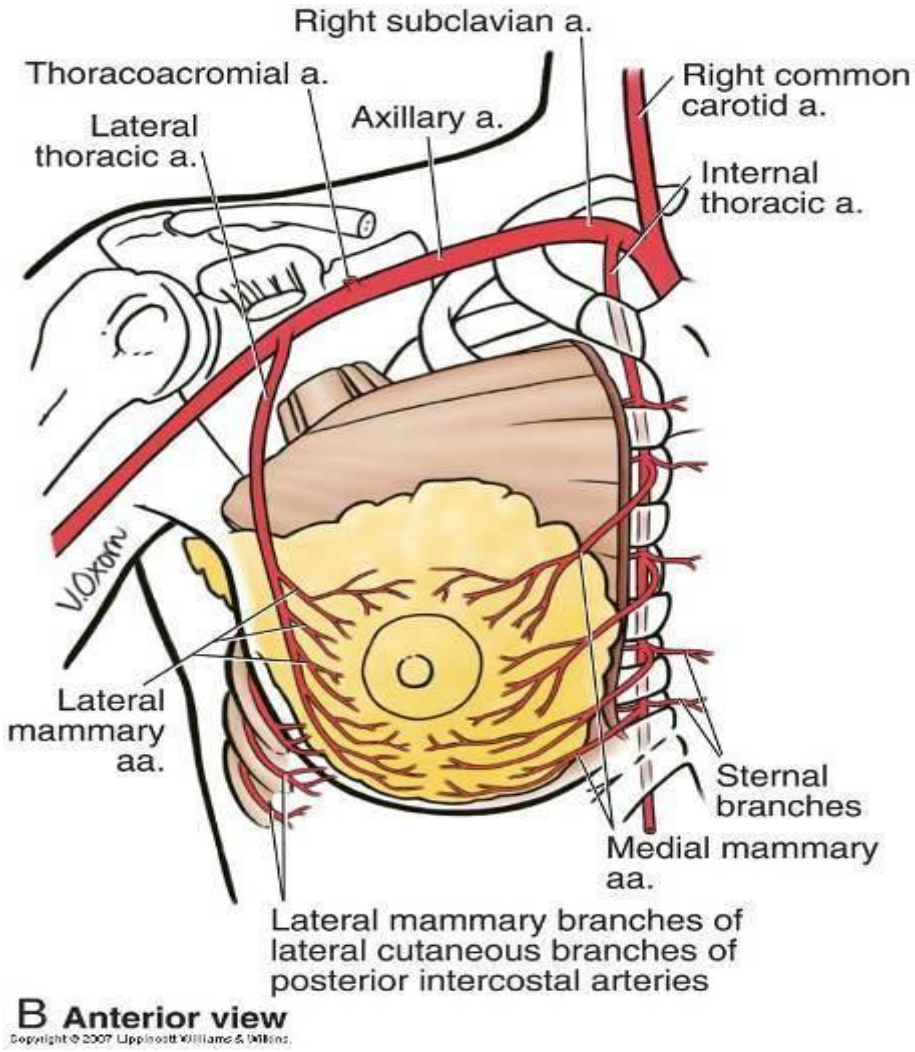
Suspensory ligament of cooper- It is a band of connective tissue which connects skin and deep fascia and anchor the breast.

ARTERY

1.Axillary artery through thoraco acromial artery, lateral thoracic artery and subscapular branches

2.Internal thoracic artery through perforating branches

3. 2nd to 4th intercostals arteries



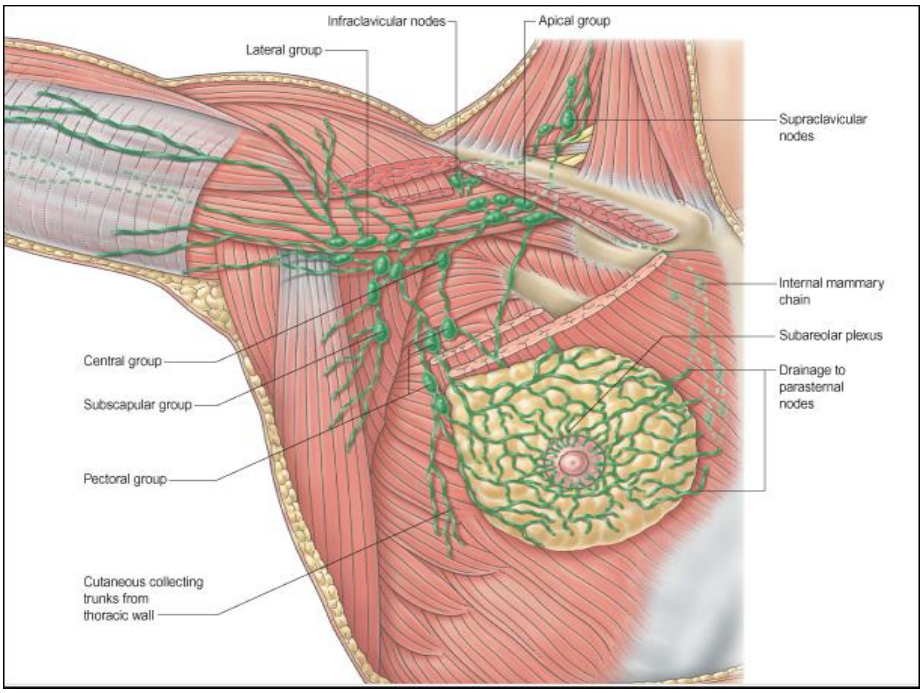
VEINS

There is circular venous plexus around the areola. Blood from this circular venous plexus and gland drains via veins accompanying correspond arteries.

LYMPHATIC DRAINAGE

There are 20 to 40 axillary nodes receive more than 75% of the lymph from the mammary gland which is grouped into pectoral, subscapular, central and apical groups and surgically these nodes described in relation to pectoralis minor. Lymphatic drainage from the the subareolar plexus of sapppey and outer quadrant of the breast takes place first to the pectoral, central and lostly to the apical nodes. The other two groups of axillary nodes viz the subscapular and lateral group may be involved in a retrograde manner. From the apical group supraclavicular group may be involved. The upper quadrant of the breast drains partly to deltopectoral nodes but mainly to the apical group. From the inner quadrant of the breast the lymph spread occurs to the internal mammary group

and to the other breast. From the lowe and inner quadrant of the breast the lymph vessels form a plexus over the rectus over the rectus sheath and pierce the costal margin to communicate with subperitoneal lymph plexus known as transcoelomic implantation .

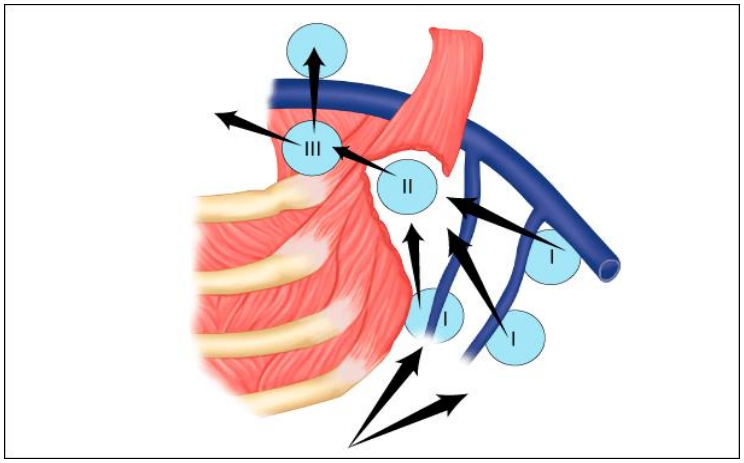


Level 1-nodes lying below pectoralis minor

Level 2-nodes behind the muscle

Level 3-nodes between pectoralis minor and lower border of clavicle.

Remainder drains into parasternal nodes.



Microstructure:

Depends on the age, time of the menstruation period, pregnancy and lactation the microstructure of breast tissues varies. Almost entire length of the ducts are lined by columnar epithelium. In the larger ducts it is arranged in two cells thick but smaller duct shows single layer of columnar or cuboidal cells. The bases of these cells in contact with numerous myoepithelial cells like other glandular epithelia. These numerous myoepithelial surrounds the ducts and alveoli and give the epithelium a bilayered appearance.

Lactiferous ducts draining each lobe of the breast enters the nipple and open as 15 to 25 orifices. Near the opening, each of these ducts is slightly expanded as a lactiferous sinus which is further dilated in lactating mothers.

Each lactiferous duct is connected to a system of ducts and lobules which is surrounded by connective tissue stroma, ultimately forms the lobe of the mammary gland.

Lobules made up of portions of the glands that has the secretory potential. Depending upon the hormonal status these structure are variable. In the mature resting mammary gland each lobules consists of a cluster of blind-ended, branched ductules whose ends lack terminal alveoli, which are the source of milk secretion in the lactating breast.

Keratinized stratified squamous epithelium replacing stratified cuboidal epithelium near the opening of lactiferous ducts in the nipple.

Nipple is internally composed of collagenous dense connective tissue and contains numerous elastic fibres. Smooth muscle cells are arranged in circular fashion are lie deep to the nipple.

ABERRATIONS OF NORMAL DEVELOPMENT AND INVOLUTION (ANDI) OF THE BREAST

It is described by the Cardiff breast clinic. Pathogenesis involves disturbance in the normal breast physiology extending from slight deviation of the normality to well defined disease process.

It includes variety of benign breast disorders happening at different periods of the reproductive periods of the females. Early, matured and involution stage of reproductive period. All disorders under ANDI should be carefully examined clinically and often USG, mammography and FNAC/core cut biopsy done to rule out malignant conditions.

It is based on three phases of normal physiology of breast.

1.lobular development 2.cyclical hormonal modifications 3.Involutions.

Pathology: This disease consists of four features essentially

1. Cyst formation-it is almost inevitable and variable in size
2. 2.fibrosi –elastic and fat tissues are replaced by dense white fibrous trabeculae. The interstitial tissue is infiltrated with chonic inflammatory cells
3. 3.hyperplasia -hyperplasia of the epithelium in the lining of the ducts and acini may occur with or without atypia

4.Papillomatosis-The epithelial hyperplasia may be so extensive that it results in papillomatous overgrowth within the ducts.

MANIFESTATION OF ANDI: The commonest manifestation of ANDI are cyclical pain and nodularity.when when pain is a prominent symptom. This

should be assessed apart from nodularity. Such pain is classified unto cyclical or premenstrual mastagia and non cyclical mastagia. Cyclical mastalgi is

Related to ANDI and noncyclical mastalgia is not related to ANDI. It is usually due to musculoskeletal origin of the chest wall or it may be associated with inflammatory episodes caused by duct ectasia or periductal mastitis. Keep in mind that persistent , localized pain or discomfort may be a symptom of cancer.

Nodularity or lump of the breast is the most common symptom. It may be associated with pain. Sometimes the pain only draw the patient attention to lump in breast. These lumps usually located in the upper and outer quadrant of the breast and lumps in these areas are noticed easily than the lumps located in the centre and inner quadrant of the breast. These lumps become more larger and painful during premenstrually. Eventhough it is difficult for the patient to judge whether the swelling is gradually increase in size or not but if the patients tell that the lump fluctuate in size is particular to this condition and excludes

carcinoma breast . lumps may be single or multiple and may be sudden in onset. Lumps are often cyst and changes in secretory activity of breast leads give to rise of such cyst. Cyst may be single, multiple and vary in size. Cysts are usually smooth, round and variable in consistency . Fluctuation can be elicited if the cyst are located superficially and very tense cyst is not fluctuant and very hard. Diffuse nodularity is often bilateral and found mainly in the upper and outer quadrant. If the patient first came at menstrual period better to Reexamine the patient in first half of the menstrual period.

Focal nodularity must be examined properly to rule out the carcinoma breast.

EARLY REPRODUCTIVE AGE GROUP (15-25 YRS)

Normal lobule development may present as aberration as FA. If it is more than 5cm it is called giant fibroadenoma as a diseased status.

Normal stroma may develop juvenile hypertrophy as aberration and multiple fibroadenoma

IN MATURE REPRODUCTIVE AGE GROUP (25 TO 40 YRS)

Exagerrated normal cyclical hormonal effect on stroma and on glands may present as aberration cause generalised enlargement of the mammary gland. Its diseased status is cyclical mastalgia with nodularity also known as fibrocystadenosis.

INVOLUTION AGE GROUP (40-55 YRS)

LOBULAR INVOLUTION with adenosis, microcyst, fibrosis, apocrine metaplasia and eventual aberrations as macrocyst and cystic disease of the breast. Macrocyst is an ANI.sclerosing adenosis is also a type of aberration.

DUCTAL IVOLUTION may cause ductal dilatation and nipple discharge as aberration. Later disease status develops with bacterial infection, periductal mastitis, mammary duct fistula and non lactational brest abscess. Partial nipple retraction may be caused by periductal fibrosis.

EPITHELIAL CHANGES leads into epithelial hyperplasia and atypia.

Table 17-3 ANDI Classification of Benign Breast Disorders			
	Normal	**Disorder**	**Disease**
Early reproductive years (age 15–25 y)	Lobular development	Fibroadenoma	Giant fibroadenoma
	Stromal development	Adolescent hypertrophy	Gigantomastia
	Nipple eversion	Nipple inversion	Subareolar abscess
			Mammary duct fistula
Later reproductive years (age 25–40 y)	Cyclical changes of menstruation	Cyclical mastalgia	Incapacitating mastalgia
		Nodularity	
	Epithelial hyperplasia of pregnancy	Bloody nipple discharge	
Involution (age 35–55 y)	Lobular involution	Macrocysts	–
		Sclerosing lesions	
	Duct involution		
	Dilatation	Duct ectasia	Periductal mastitis
	Sclerosis	Nipple retraction	–
	Epithelial turnover	Epithelial hyperplasia	Epithelial hyperplasia with atypia

FIBROADENOMA

Fibroadenoma (FA) or adenofibroma is a benign tumor composed of fibrous tissue and epithelial elements. It is a common cause of discrete, firm, and mobile lump in breast between 15 to 25 yrs old age group.

It is considered asan aberrations in 'development and involution of ductotubular tissue' in the breast and not a true neoplasm.

It begins as a hyperplasia of the lobules from the terminal ductal lobular units which progressively increase in size from 1 to 3 cm.

The main symptom of fibroadenoma is painless lump in the breast. FA is a slow growing tumour and remains more or less same size for a quite long time. It may occurs anywhere within the breast tissue but more oftenly seen in lower half of the breast than the upper half.

On examination , the sweeling is not tender and without any temperature any rise in temperature. It is very smooth,firm and contains well defined border. This tumour is not fixed to skin or deeper structure. It is a highly mobile tumour without any tethering inside the breast substance. That is why it is often called a " breast mouse" or "a floating tumor" . There is no enlargement of axillar lymph nodes. Some Most of the lesions single , discrete and static but sometimes multiple lesions can occur in the same breast or bilaterally.

Near10 – 15 % lesions disappears spontaneously over a period of 6 to 60 months on observation itself.

Fibroadenoma is considered to arise from hyperresponsiveness of lobular tissue to estrogen. Presence of estrogen receptors on tissue obtained from fibroadenoma has been described.

Hence antiestrogen ,Centchroman(Ormeloxifene)can be used to suppress the proliferation of ductolobular tissue of fibroadenoma.

Sometimes soft fibroadenomas may may undergoes cystic degeneration leading to cystadenoma which ultimately transform to cystosarcoma phylloides.

Cystosarcoma phylloides (Serocystic disease of brodie): this is real giant fibroadenoma, seen in women over the age of 40 yrs. main complaint is large swelling , though occasionally may may present as nipple discharge from the nipple. It is not malignant condition. It doesn't infiltrate the skin but the overlying skin becomes thin and tense and subcutaneous veins become prominent. This tumour is not fixed to deeper structure. Sometimes axillary nodes become rarely enlarged but mostly it is because of secondary infection.

Grossly classified as

1.soft-more cellular and often bilateral. Seen in more than 30 yrs old.

2.hard –more fibrous , common below 30 yrs

3.giant- size more than 5 cm.

Microscopically classified as

1.Intracanalicular

It contains more glands which becomes stretched into elongated spidery shapes and become indented by fibrous tissue. This type of fibroadenoma are soft and larger in size. Which occurs in middle aged females between 35 to 50 yrs.

2.Pericanalicular

Pericanalicular FA which is made up of fibrous tissue surrounding small tubular glands. This type of FA is small and hard. Which occurs in young females between 15 to 35 yrs old.

Clinically presents as painless swelling in one of the breast quadrant which is smooth, nontender, firm, well localised and freely moves within the breast

Juvenile fibroadenoma- seen in adolescent girls. It shows rapid growth with stromal and epithelia hyperplasia but doesn't show alteration in the stromal epithelial balance/ cellular atypia/ periductal cellular concentration. Clinically it mimics phylloides but doesn't turn to phylloides or carcinoma.

Complex fibroadenoma- it is a typical FA with fibrocystic changes like cyst formation, apocrine metaplasia, sclerosing adenosis. It occurs in old age groups. Occasionally turn into malignancy. Core biopsy needed to confirm the condition.

Investigations

1.Mammography 2.FNAC 3.USG

Indication for surgery

1.size > 3 cm 2.multiple 3.giant type 4.recurrence 5.cosmesis

6. Complex type 7.family history of ca breast.

Surgery:

Enucleation is done under general anaesthesia

Types of incision

1.webster `s incision- circumareolar incision

2. Gaillard Thomas incision-submammary incision.

Conservative management of FA:

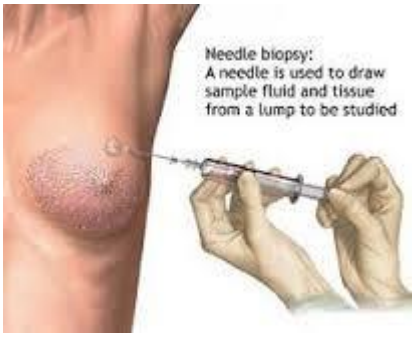
Patient under 30 yrs old doesn't require excision unless associated with suspicious cytology, or if it is >3cm size, or patient desires the lump to be removed.

For these patients regular follow-up with usg at 6monthly interval with simple observation is enough.

FINE NEEDLE ASPIRATION CYTOLOGY (FNAC)

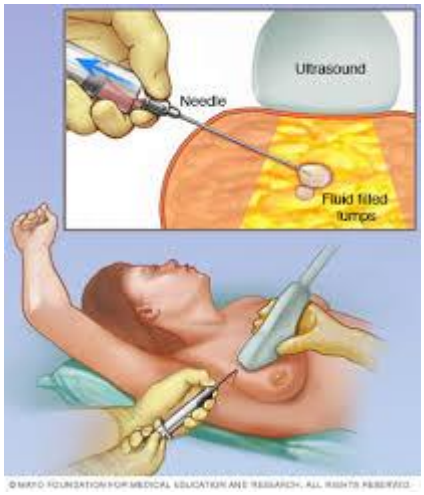
It is the least invasive method to obtain a cell diagnosis which is rapid and accure if both cytologist and operator are experienced but false negative may occur. This procedure involves aspiring cells and attendant fluid with a small bore needle, followed by cytologic examination of the stained smear. This method is mostly useful for readily palpable lesions in sites such as thyroid, lymphnode and breast. Although it has some difficulties, such as small sample size and sampling errors, in experienced hands it is extremely rapid, reliable and useful. Modern imaging techniques like usg permit extension of the method to lesions in deep seated structures like pelvic lymph node .

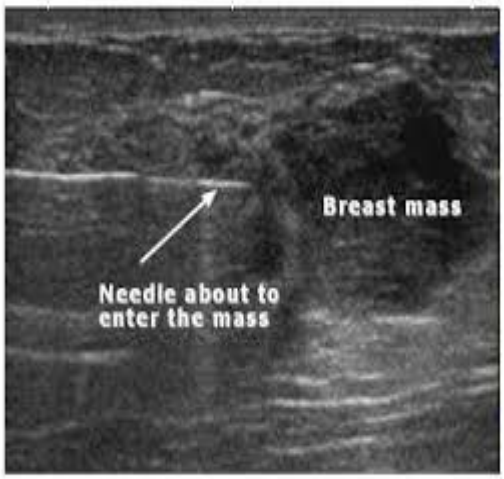
It can be done with 22 gauge needle. With the lump held properly, the needle is passed multiple times into the lump with negative pressure continuous aspiration till obtaining adequate material through the needle. Then needle witsyringe is removed without negative pressure.



The aspirate is properly prepared over the slide for cytological examination using 100% alcohol. Cytology is studied after staining it under microscopy.

Usg guided fnac: useful when the breast lump is not papable clinically, very deeply located and difficult to hold





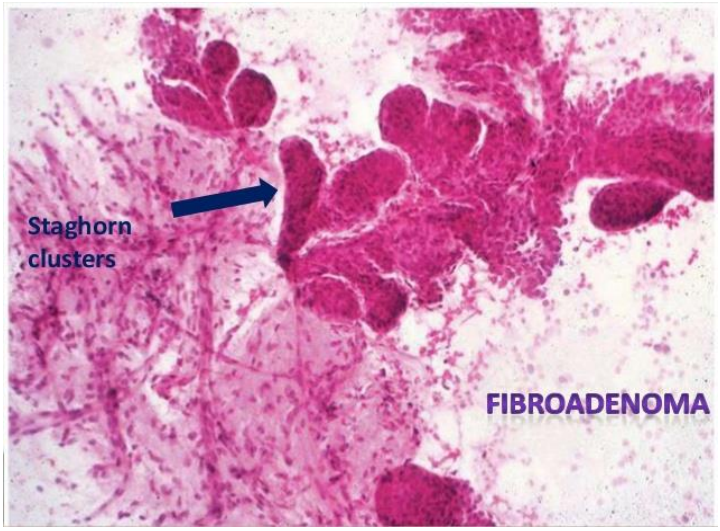
FNAC picture of fibroadenoma:

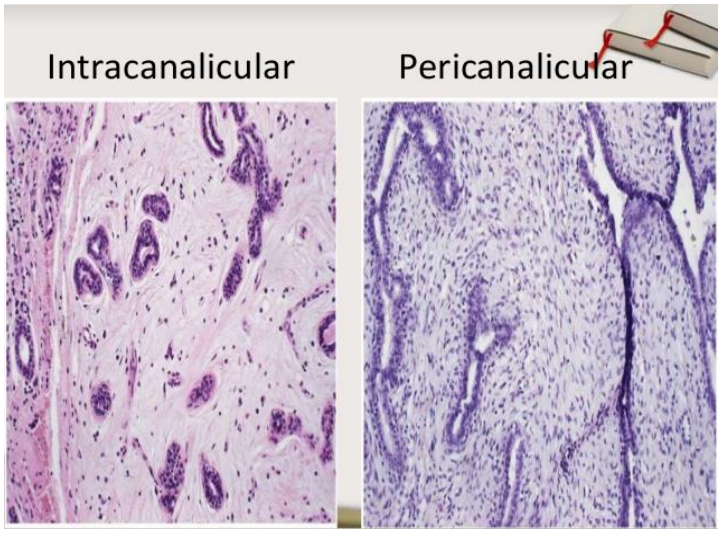
1.A high yield of cells, myxoid substance & some macroscopically visible tissue fragment

2.Large , branching sheets of bland epithelial cells(staghorn pattern of epithelial cells)

3.numerous single, bare bipolar nuclei

4.Fragments of fibromyxoid stroma.





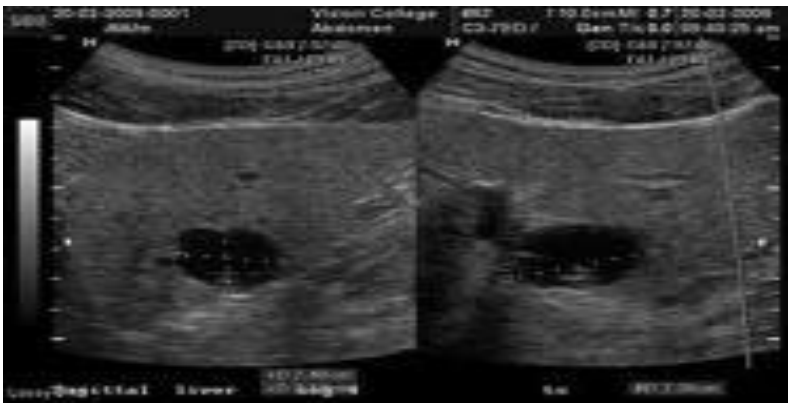
Large needle biopsy -Sampling error decreases as the as per biopsy volume increases and using 8G or 11G needles allows more tissue to be taken.

ULTRASONOGRAM (USG)

Ultrsound is inexpensive, quick, reliable and non invasive and it is the initial investigation of choice for wide range of clinical problems.usg is technically demanding and it need experienced operator to maximise the diagnostic reliability. Inspite in the advancement in technology, there are still problem with gas because it reflects sound completely and in obese patients hence both are unsuitable for ultrasonagram. Ultrasound is based on the generation of high frequency sound waves, usually between 3 to 7 MHz. Recent range of ultrasound includes probes measuring only millimetres and operating at 20 MHz.

It is useful to identify whether the lump is cystic or solid. Particularly useful in patients with dense breast. Usg is useful to localise impalpable areas of breast pathology. It is not useful as a screening tool.

FA appears oval on usg and their width is larger than anteroposterior diameter. Well circumscribed margins with gentle lobulations present .



Internal echogenicity may be homogenous but finding may range from isoechoic to hypoechoic. The through transmission of the tumour is variable.

Thin echogenic capsule is typical of FA which denotes the lesion is benign. This

thin capsule is not true capsule ,it s a pseudocapsule which is formed by compression of adjacent structures

By using color –flow Doppler or power doppler imaging the distribution and vascularity of FA is highly variable hence vascularity of breast solid masses doesn’t help to distinguish a cancer from FA.

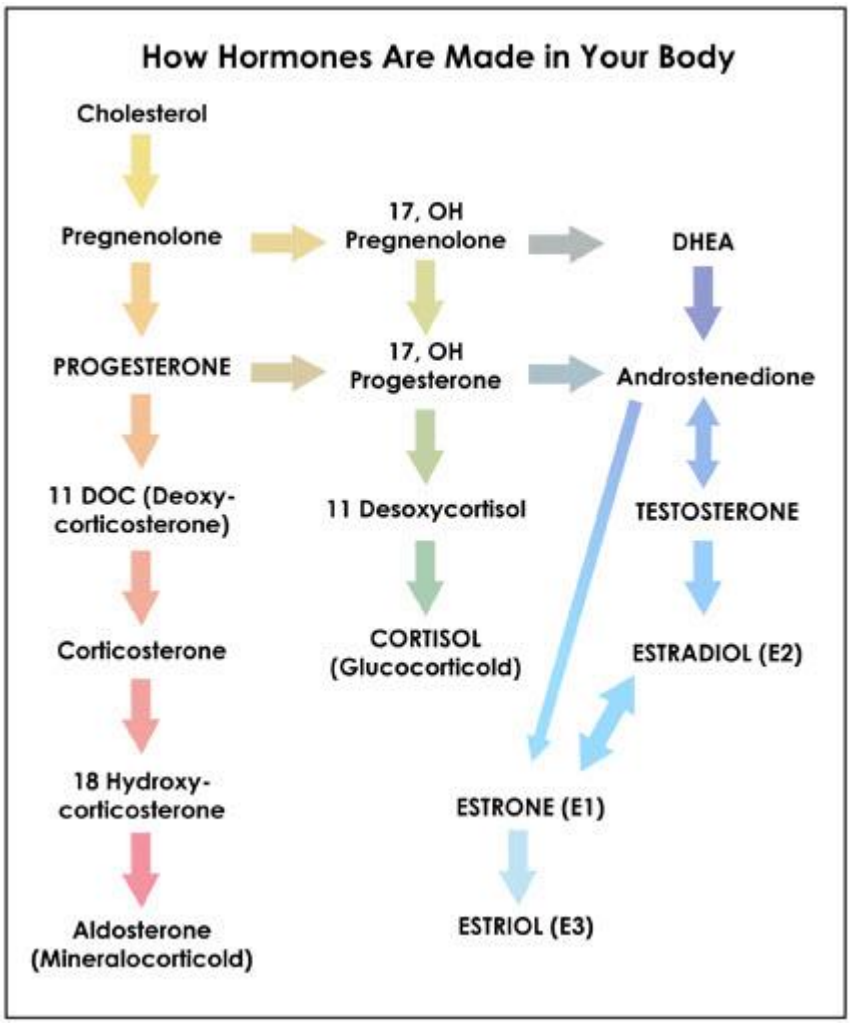
ESTROGENS

It is a female sex hormones. Mainly synthesized from the ovaries. The most potent natural estrogen for both estrogen recptors (ERα,ERβ) is 17β estradiol followed by estrone and estriol. Each molecule contains a phenolic A ring with a hydroxyl group at carbon 3 and a β-OH or ketone in position 17 of ring D.

The phenolic A ring is responsible for selective affinity for both receptors. Ethinyl substitutions at C17 position imcreases oral potency by blocking first passs metabolism in liver.

NATURAL ESTROGEN

Estradiol is the major estrogen synthesized from the ovary. It is secreted from corpus luteum, graafian follicle and placenta which is produced from cholesterol.



Estradiol is immediately oxidized to estrone in the liver . Estrone is hydroxylated to estriol. All the three hormones which mentioned above are found in the blood but among these estrdiol is the high potent estrogen hormone.

In postmenopausal women, the principle source of circulating estrogen is adipose tissue stroma, where estrone is synthesized from dehydroepiandrosterone secreted by adrenals.

REGULATION OF SECRETION:

Menstruating women shows daily secretion of estrogen 10 to 100 µg depends on the phase of menstrual cycle. Graafian follicle secretes estrogen under the influence of FSH and its blood level increases during the follicular phase. Because of preovulatory FSH surge , estrogen rises transiently further. After ovulation corpus luteum secrets estrogen till 2 days before to menstruation.

Estrogen exhibits negative feedback action on FSH and also on LH at the higher concentrations in the blood.

ACTIONS:

1. Sex organs- It brings pubertal changes in the females including growth of vagina, fallopian tubes and uterus and it is responsible for proliferation endometrim in the preovulatory phase .

   Even in the absence of progesterone withdrawal of estrogen itself can cause menstrual bleeding

2. Secondary sexual characters- Estrogen produced after puberty leads to growth of breast by inducing proliferation of stroma , duct and accumulation of fat . it is also responsible for axillary and pubic hair growth and feminine body structures.
3. Metabolic effects – it is a anabolic hormone and involved in maintaining bone mass primarily by inhibiting bone resorption. It supports positive calcium balance by inducing hydroxylase enzyme which involved in production of active form of vitamin D3.

ESTROGEN RECEPTORS:

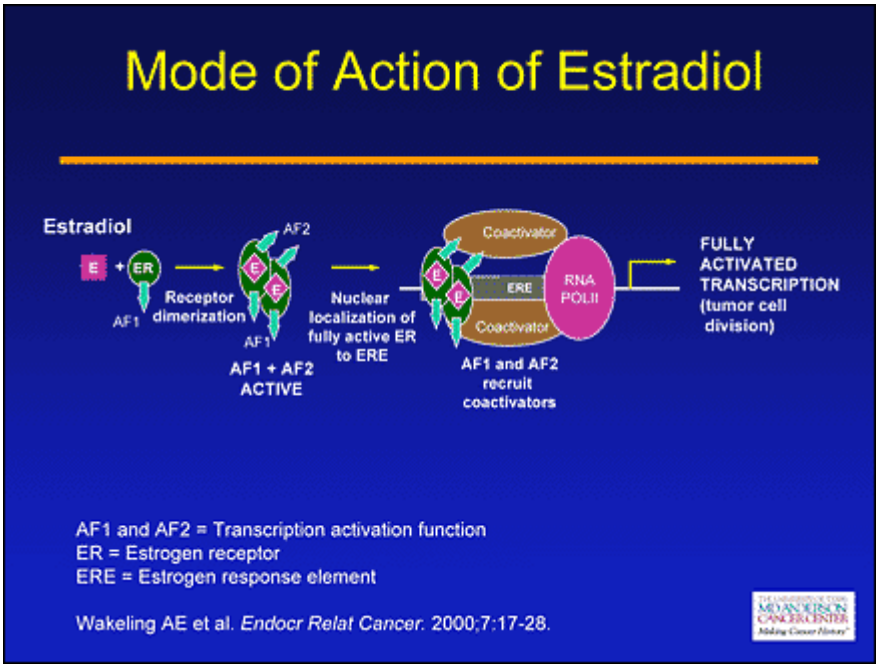
The two estrogen recptors gene are located on separate chromosomes.ESR1 encodes ERα, and ESR2 encodes ERβ. Both estrogen receptors are estrogen-dependent nuclear transcription factors that have different tissue tissue tissue distributions and transcriptional regulatory effects on a wide number of target genes.

Two types of estrogen receptors identified. 1.ERα 2.ERβ. Most of the tissues has both subtypes. ERα predominantly seen in breast, uterus, vagina, hypothalamus, and blood vessels. ERβ predominantly seen in ovaries in female and prostate in males. Estradiol binds with both receptors equally.

MECHANISM OF ACTION

Estrogen bind to particular nuclear receptors and exhibits specific effect by regulating protein synthesize. ER are found in female female sex organs, liver, pituitary,heart, cns, bones. When it binds to the ligand binding domain it leads to receptor dimerization and interaction with ERE of target genes. Gene transcription is promoted by certain coactivator proteins. When estrogen antagonist bind the receptor get a different conformation and interact with other corepressor proteins

inhibiting gene transcriptions

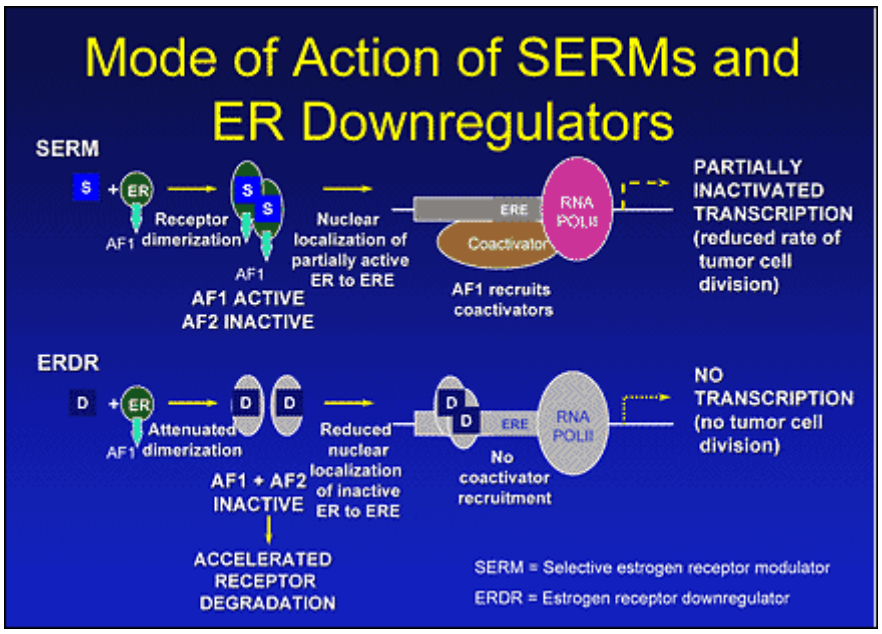


THERAPEUTIC USES- The two major uses ofestrogens are for menopausal hormone therapy (MHT) and as components of combination oral contraceptives

Menopausal Hormone Therapy.-The established benefits of estrogen therapy in postmenopausal women include amelioration of vasomotor symptoms and the prevention of bone fractures and urogenital atrophy.

SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERM)

It is a synthetic molecule. SERM can bind to both estrogen receptors and exhibits both estrogen agonist and antagonist action depends upon the target tissue.



The pharmacological goal of these drugs is to produce beneficial estrogenic actions in certain tissues like bone , brain and liver during postmenopausal hormone therapy but antagonist activity in tissues such as breast and endometrium where estrogen action might be deleterious. Currently approved

drugs in the USA are tamoxifen citrate, raloxifene hydrochloride and toremifene , which is chemically related and has similar actions to tamoxifene. Tamoxifene and toremifene are used for the treatment of breast cancer. Raloxifene is used primarily for the prevention and treatment of osteoporosis and to reduce the risk of invasive breast cancer in high risk postmenopausal women.

ORMELOXIFENE (CENTCHROMAN)

It is a nonhormonal nonsteroidal antiestrogen (Selective estrogen receptor modulator, SERM) drug produced by the Central Drug Research Institute, Lucknow, India.

It has weak agonist action on endometrium and strong antagonist action on breast ductolobular epithelium . Well absorbed from the GI tract. Peak serum levels attained in 4 hrs. widely distributed in body tissues with little affinity to plasma proteins .Currently used as contraceptive and for DUB . centchroman has been available in india for birth control since 1990.It is marketed in the trade name as saheli, centron, sevista and novex.

ADVERSE EFFECTS:

Only significant adverse effect is menstrual abnormality.Others are nausea, headache, rise in BP, Weight gain. Menstrual periods will resume at the end of 12 weeks.

Table 16.1 Variety of therapeutic targets in which established SERMs are used in comparison with estrogens

Therapy	*Hot flashes*	*Genital atrophy*	*Endometrial proliferation*	*Ovulation*	*Osteoporosis*	*Breat cancer*	*CVD*
Estrogen* ERT/HRT	↓	↓	NA	NA	↓	↑	↑
Clomifen	NA	↑	↓	↑	NA	NA	NSC
Tamoxifen	↑	↑	↑	NA	↓	↓	↑
Raloxifene	↑	NSC	↓	NA	↓	↓	↑
Genistein	↓	↓	NSC	NA	↓	NSC	↓
Centehroman	NA	NSC	NSC	NSC	↓	↓	NSC

* ERT alone not used without hysterectomy
CVD = Cardiovascular disease including Deep Venous Thrombosis
NA = Not applicable in the clinical situation
NSC = No significant change

Contraindications

1.Hypersensitivity to Ormeloxifene

2.Renal impairment

3.Hepatic impairment

4.Jaundice

5.Polycystic ovarian disease

6.Chronic cervicitis

7.Cervical hyperplasia

8.Tuberculosis.

OBSERVATIONS AND RESULTS

OBSERVATIONS AND RESULTS

The collected data was analysed with SPSS 16.0 version.To describe about the data descriptive statistics frequency analysis, percentage analysis were used for categorical variables and the mean & S.D were used for continuous variables. To find the significant difference between the bivariate samples in Independent groups (Study group & Control group) Unpaired sample t-test was used. For the repeated measures (Volume zero day ,12th week & 24th week) the Repeated measures of ANOVA with adjustment for multiple comparisons to control the type I error, the Bonferroni test was used.To find the significance in categorical data Chi-Square test was used. In all the above statistical tools the probability value .05 is considered as significant level.

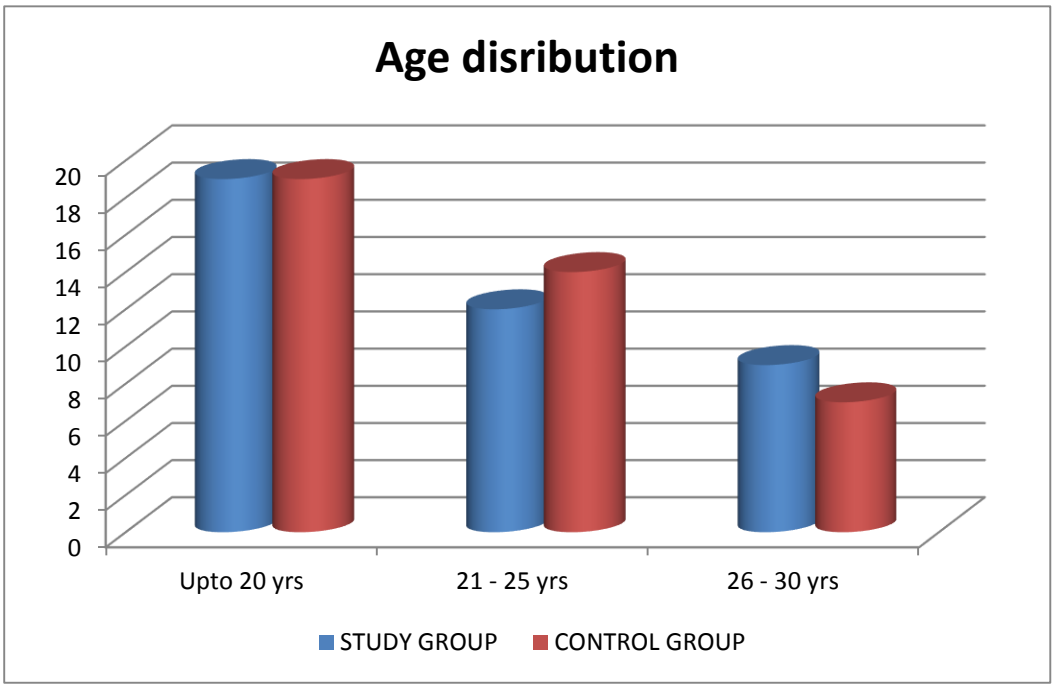
P - Value	Highly Significant at P ≤ .01

P - Value	Significant at P ≤ .05

P - Value	No Significant at P ≥ .05

Agerange * SC Crosstabulation

			SC		
			STUDY GROUP	CONTROL GROUP	Total
Agerange	Upto 20 yrs	Count	19	19	38
		% within SC	47.5%	47.5%	47.5%
	21 - 25 yrs	Count	12	14	26
		% within SC	30.0%	35.0%	32.5%
	26 - 30 yrs	Count	9	7	16
		% within SC	22.5%	17.5%	20.0%
Total		Count	40	40	80
		% within SC	100.0%	100.0%	100.0%

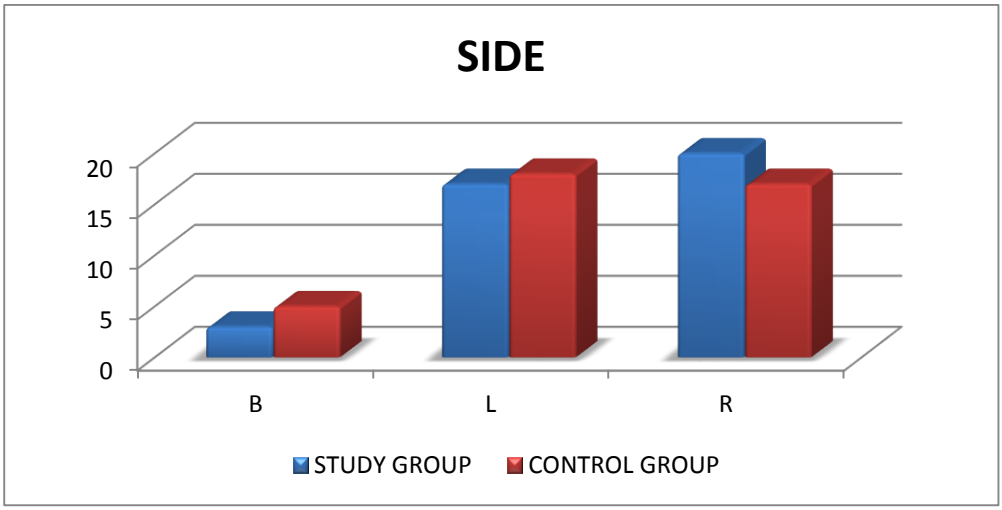

Age disribution
20
18
16
14
12
10
8
6
4
2
0
Upto 20 yrs
21 - 25 yrs
26 - 30 yrs
STUDY GROUP
CONTROL GROUP

			SC		
			STUDY GROUP	CONTROL GROUP	Total
SIDE	B	Count	3	5	8
		% within SC	7.5%	12.5%	10.0%
	L	Count	17	18	35
		% within SC	42.5%	45.0%	43.8%
	R	Count	20	17	37
		% within SC	50.0%	42.5%	46.3%
Total		Count	40	40	80
		% within SC	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	.772[a]	2	.680
Likelihood Ratio	.777	2	.678
N of Valid Cases	80		

a. 2 cells (33.3%) have expected count less than 5. The minimum expected count is 4.00.


SIDE
20
15
10
5
0
B
L
R
STUDY GROUP
CONTROL GROUP

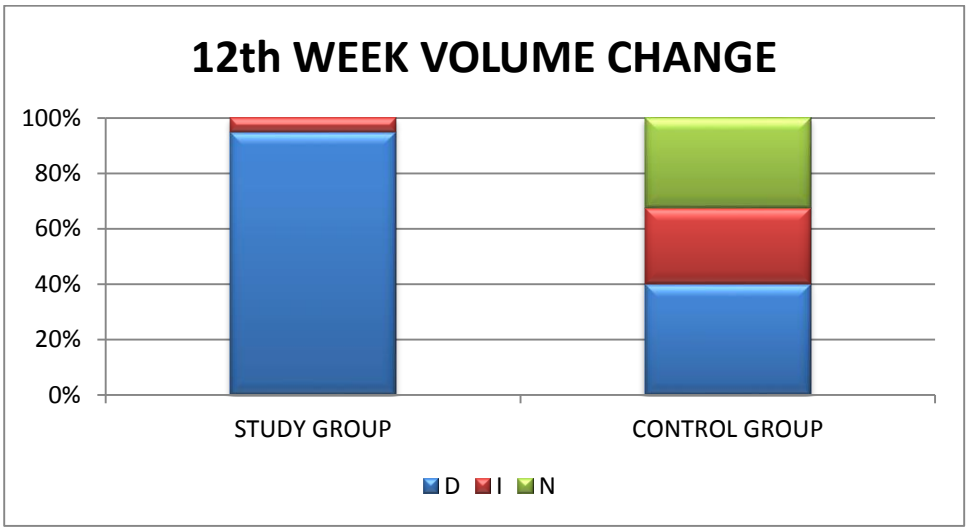
Crosstab

			SC		
			STUDY GROUP	CONTROL GROUP	Total
12WEEKS VOLUME CHANGE	D	Count	38	11	44
		% within SC	95.0%	27.0%	61.3%
	I	Count	2	16	23
		% within SC	5.0%	40.0%	22.23%
	N	Count	0	13	13
		% within SC	0.0%	32.5%	16.3%
Total		Count	40	40	80
		% within SC	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	28.194[a]	2	.000
Likelihood Ratio	34.110	2	.000
N of Valid Cases	80		

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 6.50.


12th WEEK VOLUME CHANGE
100%
80%
60%
40%
20%
0%
STUDY GROUP
CONTROL GROUP
D
I
N

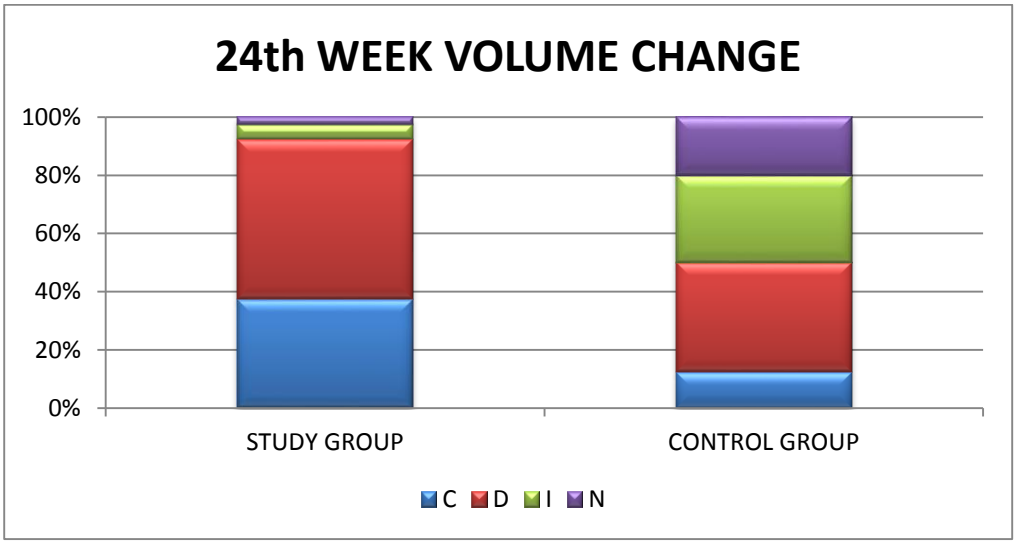
Crosstab

			SC		
			STUDY GROUP	CONTROL GROUP	Total
24WEEKS VOLUME CHANGE	C	Count	15	5	20
		% within SC	37.5%	12.5%	25.0%
	D	Count	22	6	37
		% within SC	55.0%	15%	35%
	I	Count	2	21	14
		% within SC	5.0%	52.5%	28.5%
	N	Count	1	8	9
		% within SC	2.5%	20.0%	11.3%
Total		Count	40	40	80
		% within SC	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	18.912[a]	3	.000
Likelihood Ratio	20.687	3	.000
N of Valid Cases	80		

a. 2 cells (25.0%) have expected count less than 5. The minimum expected count is 4.50


24th WEEK VOLUME CHANGE
100%
80%
60%
40%
20%
0%
STUDY GROUP
CONTROL GROUP
C
D
I
N

MENSTRUAL ABNORMALITY * SC

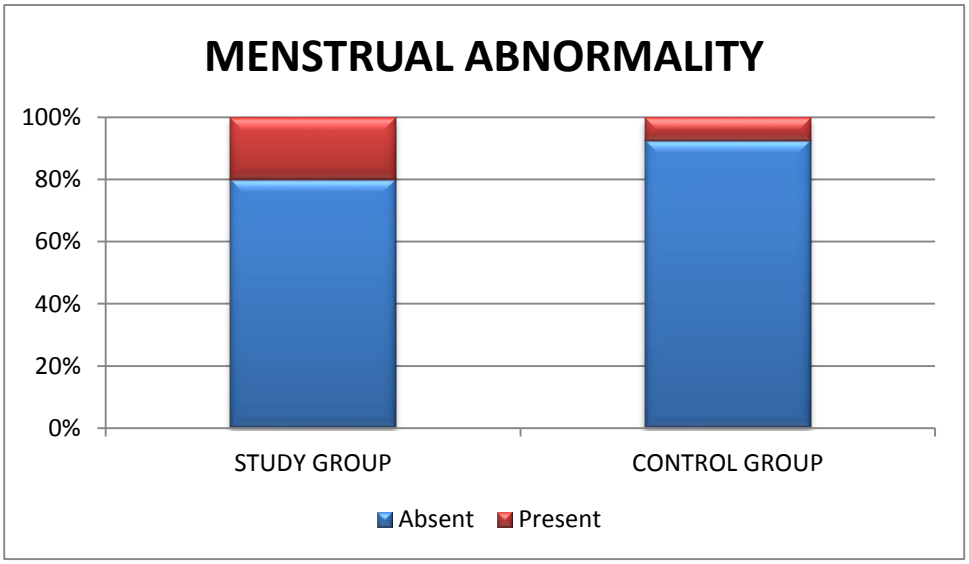
Crosstab

			SC		
			STUDY GROUP	CONTROL GROUP	Total
MENSTRUAL ABNORMALITY	Absent	Count	32	37	69
		% within SC	80.0%	92.5%	86.3%
	Present	Count	8	3	11
		% within SC	20.0%	7.5%	13.8%
Total		Count	40	40	80
		% within SC	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	2.635[a]	1	.105		
Continuity Correction[b]	1.686	1	.194		
Likelihood Ratio	2.721	1	.099		
Fisher's Exact Test				.193	.096
Linear-by-Linear Association	2.602	1	.107		
N of Valid Cases	80				

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 5.50.
b. Computed only for a 2x2 table


MENSTRUAL ABNORMALITY
100%
80%
60%
40%
20%
0%
STUDY GROUP
CONTROL GROUP
Absent
Present

HEADACHE * SC

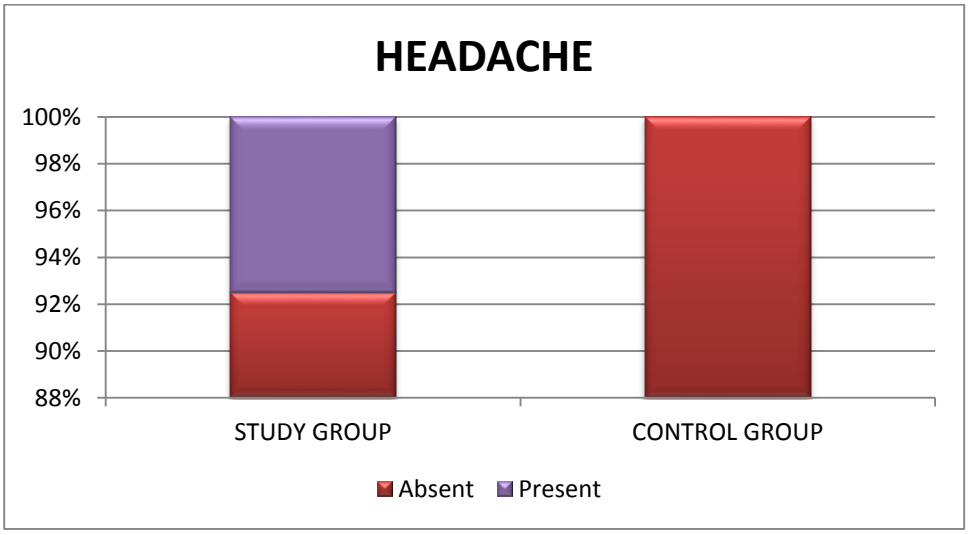
Crosstab

			SC		
			STUDY GROUP	CONTROL GROUP	Total
HEADACHE	Absent	Count	37	39	76
		% within SC	92.5%	100.0%	96.2%
	Present	Count	3	0	3
		% within SC	7.5%	0.0%	3.8%
Total		Count	40	39	79
		% within SC	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	3.040[a]	1	.081		
Continuity Correction[b]	1.334	1	.248		
Likelihood Ratio	4.199	1	.040		
Fisher's Exact Test				.241	.125
Linear-by-Linear Association	3.002	1	.083		
N of Valid Cases	79				

a. 2 cells (50.0%) have expected count less than 5. The minimum expected count is 1.48.
b. Computed only for a 2x2 table


HEADACHE
100%
98%
96%
94%
92%
90%
88%
STUDY GROUP
CONTROL GROUP
Absent
Present

NAUSEA * SC

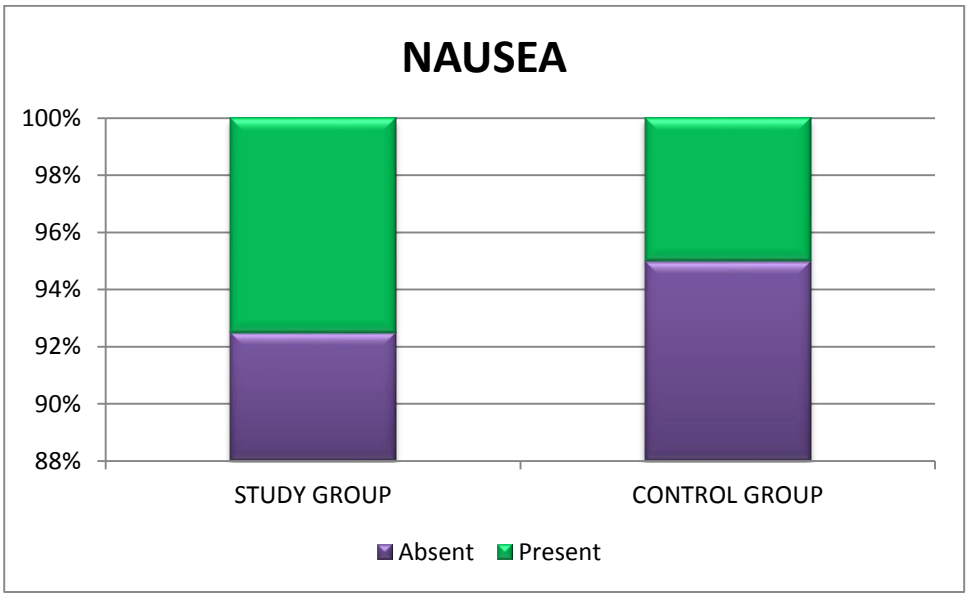
Crosstab

			SC		
			STUDY GROUP	CONTROL GROUP	Total
NAUSEA	Absent	Count	37	38	75
		% within SC	92.5%	95.0%	93.8%
	Present	Count	3	2	5
		% within SC	7.5%	5.0%	6.3%
Total		Count	40	40	80
		% within SC	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.213[a]	1	.644		
Continuity Correction[b]	0.000	1	1.000		
Likelihood Ratio	.215	1	.643		
Fisher's Exact Test				1.000	.500
Linear-by-Linear Association	.211	1	.646		
N of Valid Cases	80				

a. 2 cells (50.0%) have expected count less than 5. The minimum expected count is 2.50.
b. Computed only for a 2x2 table


NAUSEA
100%
98%
96%
94%
92%
90%
88%
STUDY GROUP
CONTROL GROUP
Absent
Present

SC = STUDY GROUP

Descriptive Statistics[a]

	Mean	Std. Deviation	N
DAY0VOLUME	8.718	3.6032	40
12 WEEKSVOLUME	2.560	3.1857	40
24 WEEKSVOLUME	1.865	3.9441	40

a. SC = STUDY GROUP

Mauchly's Test of Sphericity[a,b]

Measure: MEASURE_1

		Within Subjects Effect
		VOLUME
Mauchly's W		.176
Approx. Chi-Square		65.968
df		2
Sig.		.000
Epsilon[c]	Greenhouse-Geisser	.548
	Huynh-Feldt	.552
	Lower-bound	.500

Tests the null hypothesis that the error covariance matrix of the orthonormalized transformed dependent variables is proportional to an identity matrix.

a. SC = STUDY GROUP

b. Design: Intercept
Within Subjects Design: VOLUME

c. May be used to adjust the degrees of freedom for the averaged tests of significance. Corrected tests are displayed in the Tests of Within-Subjects Effects table.

Tests of Within-Subjects Effects[a]

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
VOLUME	Sphericity Assumed	1138.061	2	569.031	79.737	.000
	Greenhouse-Geisser	1138.061	1.097	1037.785	79.737	.000
	Huynh-Feldt	1138.061	1.105	1030.368	79.737	.000
	Lower-bound	1138.061	1.000	1138.061	79.737	.000
Error(VOLUME)	Sphericity Assumed	556.632	78	7.136		
	Greenhouse-Geisser	556.632	42.768	13.015		
	Huynh-Feldt	556.632	43.076	12.922		
	Lower-bound	556.632	39.000	14.273		

a. SC = STUDY GROUP

Tests of Within-Subjects Contrasts[a]

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
VOLUME	Linear	939.135	1	939.135	81.909	.000
	Quadratic	198.926	1	198.926	70.868	.000
Error(VOLUME)	Linear	447.160	39	11.466		
	Quadratic	109.472	39	2.807		

a. SC = STUDY GROUP

Pairwise Comparisons[a]

Measure: MEASURE_1

(I) VOLUME		Mean Difference (I-J)	Std. Error	Sig.[c]	95% Confidence Interval for Difference[c]	
					Lower Bound	Upper Bound
1	2	6.157*	.676	.000	4.466	7.849
	3	6.852*	.757	.000	4.958	8.747
2	1	-6.157*	.676	.000	-7.849	-4.466
	3	.695*	.200	.004	.195	1.195
3	1	-6.852*	.757	.000	-8.747	-4.958
	2	-.695*	.200	.004	-1.195	-.195

Based on estimated marginal means

*. The mean difference is significant at the .05 level.

a. SC = STUDY GROUP c. Adjustment for multiple comparisons: Bonferroni.

SC = CONTROL GROUP

Descriptive Statistics[a]

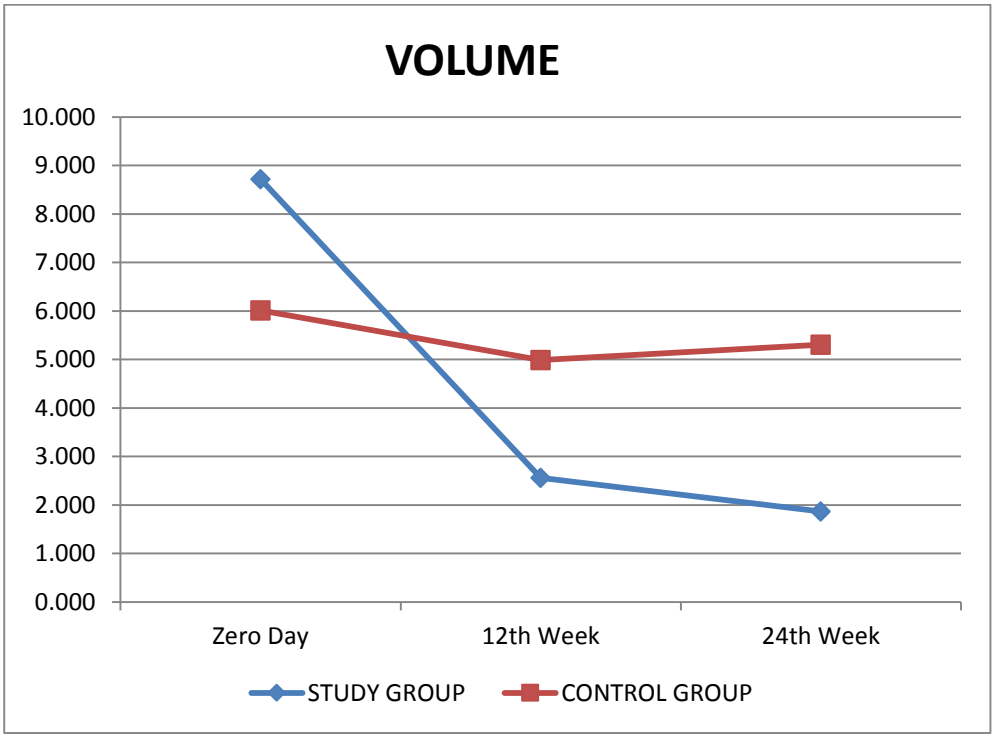
	Mean	Std. Deviation	N
DAY0VOLUME	6.010	3.0856	40
12 WEEKSVOLUME	4.990	3.7847	40
24 WEEKSVOLUME	5.305	5.0035	40

Tests of Within-Subjects Effects[a]

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
VOLUME	Sphericity Assumed	21.822	2	10.911	2.603	.080
	Greenhouse-Geisser	21.822	1.243	17.552	2.603	.106
	Huynh-Feldt	21.822	1.264	17.262	2.603	.105
	Lower-bound	21.822	1.000	21.822	2.603	.115
Error(VOLUME)	Sphericity Assumed	326.911	78	4.191		
	Greenhouse-Geisser	326.911	48.487	6.742		
	Huynh-Feldt	326.911	49.302	6.631		
	Lower-bound	326.911	39.000	8.382		

a. SC = CONTROL GROUP


VOLUME
10.000
9.000
8.000
7.000
6.000
5.000
4.000
3.000
2.000
1.000
0.000
Zero Day
12th Week
24th Week
STUDY GROUP
CONTROL GROUP

DISCUSSION

DISCUSSION

Fibroadenoma is the most common tumour of females less than 30 yrs old and second most common neoplasm of females and 20 % of the patient shows bilateral and 20 % shows multiple FA After verifying lot of studies about the conservative management of mastalgia and benign breast conditions like fibroadenoma and fibroadenosis , I decided to do this study Instead of simple observation , if the patientt is willing since 15 % of fibroadenoma will regress spontaneously over 1 – 6 yrs observation.

According to the study " regression of fibroadenoma with centchroman: a RCT" done by praksah laxmichand and tejwani et al, was carried out in aims, department of general surgery , new delhi between nov 2004 to nov 2007 with 6 months follow-up. Study showed 31.88 % fibroadenomas in study group who

had 30 mg centchroman od for 90 days daily complete disappearance as compared to 7.69 % in control group.

52.17% fibroadenomas decreased in size in study group as compared to control group. According to my study patients had centchroman 30 mg od on alternative days .

Among 80 patients 40 patients in study group and 40 patients in control group . 8 (10%) patients showed bilateral FA presentation.

At the end of 12 weeks follow- up 38 (95%) patients showed decrease in size in study as compared to 11(27%) in control group.

At the end of 24 weeks follow-up 15 (37.5%) patients showed complete disappearance compared to 5 (12.5%) patients in control group.

22 (55%) patients showed decrease in size as compared to 6 (15%) patients in control group.

21(30%) patients in control group showed increase in size compared to study group where 2 (5%) patients showed increase in size.

8 (20%) patients showed menstruation abnormality compared to 3 (7.5%) patients in control group, it is satistically insignificant according my study.

Only 3 (7.5)patients showed headache in study group as compared to o patients in control group.

And 3 patients in study group complained nausea.

As already explained Fibroadenoma is considered to arise due to hyperresponsiveness of lobular tissue to estrogen. Presence of estrogen receptors on tissue obtained from fibroadenoma has been described. Hence Centchroman(Ormeloxifene) has been used in this study ..

But decrease in size of the FA even after 12th week (after centchroman regimen getting over) has been observed. It may be due to hit and run effect of the drug so it needs further study.

LIMITATION OF THE STUDY:

This study presents data based on 6 months follow-up only. Long term results of centchroman on recurrent and further decrease in size require further studies in future.

CONCLUSION

CONCLUSION:

1.Centchroman therapy in FA treatment showed satistifically significant regression of volume.

2. Long term results beyond 6 months needs further study

3. It is useful in patient who is willing for observation instead of Enucleation of FA

4. Patients more than 30 yrs old and young patients (<30 yrs) with suspicious histology, recurrence , family h/o carcinoma breast , anxiousness and no response to conservative management are the ideal candidate for active management as excisional biopsy (enucleation of FA).

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9. Natural History of Fibroadenomas Based on the Correlation Between Size and Patient Age
Hiroyuki Takei[1], Yuichi Iino[2],Jun Horiguchi[1], Michio Maemura[1], Takao Yokoe[2],Yukio Koibuchi[1], Tetsunari Oyama[3], Susumu Ohwada[1] and Yasuo Morishita[1]

MASTER CHART- STUDY GROUP

					DAY C	DAY I	DAY O	DAY O	12 WEEKS	12 WEEKS	12 WEEKS	12 WEEKS	12 WEEKS		24 WEEEK	24 WEEEK	24 WEEEK	24 WEEEI	24 WEEEKS	COMPLICATIONS			
SN	NAME	AGE	PATIENT	SIDE	A	B	C	VOLUME	A	B	C	VOLUME	VOLUME CHAN		A	B	C	VOLUME	VOLUME CHAN	MENSTRUAL ABNORM	HEADACI	NAUSEA	
1	SULOCHANA	18	A01	R	3	2.7	2.9	12.2	1.6	1.2	1.4	1.4	D		0	0	0	0	C	Y	Y	Y	
2	RAZEEMA	19	A02	R	2.2	1.8	2	4.1	1.7	1	1.4	1.2	D		1.2	0.8	1	0.5	D				
3	ANURADHA	20	A03	L	2.6	2.5	2.5	8.5	1.3	1.1	1.2	0.9	D		0	0	0	0	C				
4	CHITRA	19	A04	B	2	2	2	4.2	1.8	1.6	1.7	2.5	D		1	1.1	1.1	0.6	D	Y			
					2	1.8	1.9	3.6	1.4	1.2	1.3	1.1	D		1.2	1	1.1	0.7	D		Y		
5	SWATHI	20	A05	R	2.8	2.4	2.6	9.1	2.8	2.6	2.7	10.2	I		2.9	3	2.9	13.3	I				
6	REVATHI	21	A06	L	2.4	2	2.2	5.5	1.5	1.1	1.3	1.1	D		0	0	0	0	C				
7	BHARANI	24	A07	R	2.5	1.5	2	3.9	1.5	1.3	1.4	1.4	D		1.3	0.9	1.1	0.7	D	Y			
8	KEERTHIKA	22	A08	L	3	2.8	2.9	12.7	3.2	2.9	3.1	14.9	I		3.5	3.2	3.4	19	I				
9	MAHESHWARI	28	A09	B	3	2.8	2.9	12.7	1.6	1.3	1.5	1.6	D		1.4	1	1.2	0.9	D				
					2.4	2	2.2	5.5	1.2	1	1.1	0.7	D		1.2	0.8	1	0.5	D				
					2.8	2.4	2.6	9.1	1.6	1.4	1.5	1.7	D		1.6	1.2	1.4	1.4	D				
10	BHAVANI	26	A10	R	3	3	3	14	1.4	1.5	1.5	1.6	D		0	0	0	0	C	Y			
11	RAJALAKSHMI	29	A11	R	2.8	2.6	2.7	10.2	1.5	1.3	1.4	1.4	D		1.2	0.8	1	0.5	D				
12	SHABANA	19	A12	R	3	2.5	2.7	10.5	1.7	1.1	1.4	1.4	D		0	0	0	0	C				
13	AMULI	30	A13	R	2.4	1.8	2.1	4.7	1.1	1.5	1.3	1.1	D		0	0	0	0	C		Y		
				R	2.8	1.6	2.2	5.1	1.3	1	1.1	0.7	D		0	0	0	0	C				
14	SHAJINI	20	A14	R	2.7	2.6	2.6	9.5	1.2	1.1	1.2	0.8	D		1	0.8	0.9	0.4	D			Y	
15	HAMEELA BANU	21	A15	L	3	2.5	2.7	10.5	1.4	1.6	1.5	1.7	D		1.2	1	1.1	0.7	D				
16	VALLI	28	A16	R	3	3	3	14	1.7	1.3	1.5	0.7	D		0	0	0	0	C				
17	NAJEERA	19	A17	L	3	3	3	14	1.5	1.4	1.5	1.6	D		1.5	1.4	1.5	1.6	D	Y			
				L	2.5	1.8	2.1	4.9	1.5	1.1	1.3	1.1	D		1	0.7	0.9	0.3	D			Y	
18	BHUVITHA	20	A18	L	2.4	1.7	2.1	4.5	1.3	1.4	1.4	1.3	D		0	0	0	0	C				
19	JAVEENA	22	A19	R	2.7	2.6	2.7	9.8	1.5	1.3	1.4	1.4	D		1.4	0.9	1.2	0.8	D				
20	GANDHIMATHI	29	A20	L	3	2.5	2.8	10.9	3	2.5	2.8	10.1	D		3	2.2	2.6	8.9	D				
21	RAJESHWARI	22	A21	L	3	2.7	2.9	12.2	1.6	1.2	1.4	1.4	D		1.6	1.2	1.4	1.4	D	Y			
				L	2.5	2.4	2.5	7.8	1.1	0.9	1	0.5	D		1	0.8	0.9	0.4	D				

					DAY C	DAY I	DAY O	DAY O	12 WEEKS	12 WEEKS	12 WEEKS	12 WEEKS	12 WEEKS		24 WEEEK	24 WEEEK	24 WEEEK	24 WEEEI	24 WEEEKS	COMPLICATIONS		
SN	NAME	AGE	PATIENT	SIDE	A	B	C	VOLUME	A	B	C	VOLUME	VOLUME CHAN		A	B	C	VOLUME	VOLUME CHAN	MENSTRUAL ABNORM	HEADACI	NAUSEA
1	SULOCHANA	18	A01	R	3	2.7	2.9	12.2	1.6	1.2	1.4	1.4	D		0	0	0	0	C	Y	Y	Y
2	RAZEEMA	19	A02	R	2.2	1.8	2	4.1	1.7	1	1.4	1.2	D		1.2	0.8	1	0.5	D			
3	ANURADHA	20	A03	L	2.6	2.5	2.5	8.5	1.3	1.1	1.2	0.9	D		0	0	0	0	C			
4	CHITRA	19	A04	B	2	2	2	4.2	1.8	1.6	1.7	2.5	D		1	1.1	1.1	0.6	D	Y		
					2	1.8	1.9	3.6	1.4	1.2	1.3	1.1	D		1.2	1	1.1	0.7	D		Y	
5	SWATHI	20	A05	R	2.8	2.4	2.6	9.1	2.8	2.6	2.7	10.2	I		2.9	3	2.9	13.3	I			
6	REVATHI	21	A06	L	2.4	2	2.2	5.5	1.5	1.1	1.3	1.1	D		0	0	0	0	C			
7	BHARANI	24	A07	R	2.5	1.5	2	3.9	1.5	1.3	1.4	1.4	D		1.3	0.9	1.1	0.7	D	Y		
8	KEERTHIKA	22	A08	L	3	2.8	2.9	12.7	3.2	2.9	3.1	14.9	I		3.5	3.2	3.4	19	I			
9	MAHESHWARI	28	A09	B	3	2.8	2.9	12.7	1.6	1.3	1.5	1.6	D		1.4	1	1.2	0.9	D			
					2.4	2	2.2	5.5	1.2	1	1.1	0.7	D		1.2	0.8	1	0.5	D			
					2.8	2.4	2.6	9.1	1.6	1.4	1.5	1.7	D		1.6	1.2	1.4	1.4	D			
10	BHAVANI	26	A10	R	3	3	3	14	1.4	1.5	1.5	1.6	D		0	0	0	0	C	Y		
11	RAJALAKSHMI	29	A11	R	2.8	2.6	2.7	10.2	1.5	1.3	1.4	1.4	D		1.2	0.8	1	0.5	D			
12	SHABANA	19	A12	R	3	2.5	2.7	10.5	1.7	1.1	1.4	1.4	D		0	0	0	0	C			
13	AMULI	30	A13	R	2.4	1.8	2.1	4.7	1.1	1.5	1.3	1.1	D		0	0	0	0	C		Y	
				R	2.8	1.6	2.2	5.1	1.3	1	1.1	0.7	D		0	0	0	0	C			
14	SHAJINI	20	A14	R	2.7	2.6	2.6	9.5	1.2	1.1	1.2	0.8	D		1	0.8	0.9	0.4	D			Y
15	HAMEELA BANU	21	A15	L	3	2.5	2.7	10.5	1.4	1.6	1.5	1.7	D		1.2	1	1.1	0.7	D			
16	VALLI	28	A16	R	3	3	3	14	1.7	1.3	1.5	0.7	D		0	0	0	0	C			
17	NAJEERA	19	A17	L	3	3	3	14	1.5	1.4	1.5	1.6	D		1.5	1.4	1.5	1.6	D	Y		
				L	2.5	1.8	2.1	4.9	1.5	1.1	1.3	1.1	D		1	0.7	0.9	0.3	D			Y
18	BHUVITHA	20	A18	L	2.4	1.7	2.1	4.5	1.3	1.4	1.4	1.3	D		0	0	0	0	C			
19	JAVEENA	22	A19	R	2.7	2.6	2.7	9.8	1.5	1.3	1.4	1.4	D		1.4	0.9	1.2	0.8	D			
20	GANDHIMATHI	29	A20	L	3	2.5	2.8	10.9	3	2.5	2.8	10.1	D		3	2.2	2.6	8.9	D			
21	RAJESHWARI	22	A21	L	3	2.7	2.9	12.2	1.6	1.2	1.4	1.4	D		1.6	1.2	1.4	1.4	D	Y		
				L	2.5	2.4	2.5	7.8	1.1	0.9	1	0.5	D		1	0.8	0.9	0.4	D			

MASTER CHART-CONTROL GROUP

41	ARUNA	19	C41	R	2.5	2.5	2.5	8.1	2.1	1.8	1.9	3.8	D	1.7	1.2	1.5	1.5	D			
42	VENNILA	24	C42	L	3	2.8	2.9	12.7	1.4	1.3	1.4	1.3	D	0	0	0	0	C			
43	PARAMESHWARI	28	C43	R	2.4	2.4	2.4	7.2	2.4	2.4	2.4	7.2	N	2.4	2.4	2.4	7.2	N			
44	AKILA	21	C44	R	2.6	2.4	2.5	8.1	2.2	1.2	1.7	2.3	D	1.8	1	1.4	1.3	D			
45	VINDHYA	22	C45	L	2.8	2.1	2.5	6.4	2.8	2.1	2.5	7.5	I	2.8	2.1	2.5	7.6	I			
46	MIRNALINI	24	C46	B	3	2.3	2.7	9.6	3	2.3	2.7	9.6	N	3.2	2.4	2.8	11.2	I	Y		
					2.6	2	2.3	6.2	2.8	2.2	2.5	8	I	3	2.4	2.7	10	I			
					2.4	1.8	2.1	4.7	2.6	2.2	2.4	7.1	I	2.6	2.2	2.4	7.1	I			
47	RAMYA	19	C47	R	1.8	1.6	1.7	2.5	1.4	1.2	1.3	1.1	D	1.2	1	1.1	0.7	D			
48	KAVITHA	19	C48	R	2.6	1.4	2	3.8	2.6	1.4	2	3.8	N	2.6	1.4	2	4.9	D			
49	SARANYA	26	C49	L	2	1.8	1.9	3.6	2	1.8	1.9	3.6	N	2	1.8	1.9	3.6	N			
50	GAYATRI	20	C50	L	2.2	1.8	2	4.1	1.1	0.8	0.9	0.4	D	0	0	0	0	C			
51	AMIRTHA	19	C51	L	2.6	2.4	2.5	8.1	2.8	2.4	2.6	9.1	I	2.8	2.5	2.7	9.6	I			
52	JOTHILAKSHMI	19	C52	R	2.3	1.5	1.9	3.4	1.3	1	1.2	0.8	D	1	0.8	0.9	0.4	D			
53	KANAGA	20	C53	R	2	1.8	1.9	3.6	2	1.8	1.9	3.6	N	2	1.8	1.9	3.6	N			Y
54	MALINI	18	C54	R	2.4	2.2	2.3	6.3	2.4	2.2	2.3	6.3	N	2.4	2.2	2.3	4.5	D			
55	NITHIYA	28	C55	L	1.7	1.4	1.6	2	1.7	1.4	1.5	1.9	D	1.7	1.4	1.6	1.9	D	Y		
56	VANAJA	20	C56	L	1.6	1.5	1.1	1.4	1.4	1.2	1.3	1.1	D	1.2	0.8	1	0.5	D			
57	MEERA	20	C57	L	2.3	1.7	2	4.1	2.4	1.8	2.1	4.7	I	2.6	2	2.3	6.2	I			
58	ROHINI	22	C58	L	2.5	1.9	2.2	5.4	1.4	1.1	1.3	1	D	0	0	0	0	C			
59	HIRUNNISA	22	C59	B	2.9	2.4	2.7	9.8	3	2.4	2.7	10	I	3.2	2.6	2.9	12.5	I			
					3	3	3	14	3.2	3.2	3.2	17	I	3.3	3.5	3.4	20.4	I			
60	SUBBRIYA	24	C60	L	2.6	2.2	2.4	7.1	2.6	2.2	2.4	7.1	N	2.6	2.2	2.4	7.1	N			
61	RAGAVI	23	C61	L	2.5	2.5	2.5	8.1	2.5	2.5	2.5	8.1	N	2.5	2.5	2.5	8.1	N			
				L	1.8	1.7	1.8	2.9	1.8	1.7	1.8	2.8	D	1.8	1.7	1.8	2.8	D			
62	KALIYAMMA	24	C62	R	2.5	1.7	2.1	4.6	1.5	1.1	1.3	1.1	D	1.4	1	1.2	0.9	D		y	
63	RAKKAMA	20	C63	L	2.6	2.4	2.5	8.1	2.8	2.6	2.7	10.2	I	2.8	2.6	2.7	10.2	I			
64	PRABHAVATHY	18	C64	R	2.5	2.3	2.4	7.2	2.5	2.3	2.4	7.2	N	2.5	2.3	2.4	7.2	N			
65	SOWBHAKIYYAM	19	C65	L	1.7	1.7	1.7	2.6	1.8	1.8	1.8	3	I	2	2	2	4.1				
66	SIVALOSHINI	21	C66	L	1.9	1.6	1.8	2.8	1.5	1.2	1.4	1.3	D	1.4	1.1	1.3	1	D			
67	RADHALAKSHMI	25	C67	B	3	2.5	2.8	10.9	3	2.5	2.8	10.7	D	3	2.5	2.8	10.7	D			
					2.6	2.3	2.5	7.8	2.7	2.5	2.6	9.1	I	2.7	2.5	2.6	9.1	I			
					2.4	1.4	1.9	3.3	2.6	1.5	2.1	4.2	I	2.8	1.8	2.3	6	I			
68	MAIMOONA	26	C68	L	2.5	2.3	2.4	7.1	2.5	2.5	2.5	8.1	I	2.6	2.7	2.7	18	I			
69	KEERTHANA	20	C69	R	1.7	1.5	1.6	2.1	1.6	1.5	1.6	2	D	0	0	0	0	C	Y		Y
70	LALITHA	21	C70	L	2.5	2.4	2.5	7.8	2.6	2.5	2.6	8.6	I	2.7	2.6	2.7	9.7	I			
71	DEVI	18	C71	R	2.6	1.6	2.1	4.5	2.6	1.6	2.1	4.5	N	2.6	1.6	2.1	4.5	N			
72	DIVYADHARSHINI	29	C72	B	1.8	1.4	1.6	2.1	1.8	1.4	1.6	2.1	N	2	1.6	1.8	2.9	I			
					1.7	1.3	1.5	1.7	2	1.5	1.8	2.8	I	2.2	1.6	1.9	3.5	I			
73	UMAMAHESHWARI	23	C73	B	3	3	3	14	3	3.2	3.1	15.5	I	3.2	3.4	3.3	18.6	I			
					2.6	2	2.3	6.2	2.6	2.2	2.4	6.6	I	2.8	2.4	2.6	9	I			
74	DEEPTHI	20	C74	R	2.5	2.3	2.4	7.2	1.5	1.3	1.4	1.4	D	1.4	1.1	1.3	1	D			
75	PREETHI	27	C75	L	2.6	2.5	2.6	8.8	2.8	2.5	2.6	9.6	I	3	2.6	2.8	11.3	I			
76	PAVITHRA	20	C76	L	1.7	1.2	1.5	1.6	1.7	1.2	1.5	1.6	N	1.7	1.2	1.5	1.5	D			
77	YOGESHWARI	23	C77	R	2.7	1.7	2.2	5.3	1.7	1.4	1.6	1.9	D	1.3	1.1	1.2	0.9	D			
78	PUNITHA	19	C78	R	2.8	2.4	2.6	9.1	2.8	2.6	2.7	10.2	I	3	2.7	2.9	12	I			
					2.8	2	2.4	7	3	2.2	2.6	8.9	I	3	2.4	2.7	10.1	I			
79	PRIYA	20	C79	R	2.5	1.5	2	3.9	1.4	1.1	1.3	1	D	0	0	0	0	C			
80	POORVIKA	27	C80	R	2.7	1.7	2.2	5.3	2.7	1.7	2.2	5.3	N	2.7	1.7	2.2	5.3	N			

a-largest dimension b-dimension at right angle to a c=a+b/2 VOLUME=Axbxcx.52

R-RIGHT L-LEFT B-BILATERAL

D-DECREASE N-NO CHANGE I-INCREASED C-COMPLETE DISAPPEARANCE Y-YES

A1-A40= STUDY GROUP (CENTCHROMAN)

INSTITUTIONAL ETHICAL COMMITTEE, STANLEY MEDICAL COLLEGE, CHENNAI-1

Title of the Work : Regression of Fibroadenoma in response to Centchroman Theraphy.

Principal Investigator : Dr. Sabrimalai. P
Designation : PG in MS (General Surgery)

Department : Department of General Surgery
Government Stanley Medical College,
Chennai-01

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 13.01.2015 at the Council Hall, Stanley Medical College, Chennai-1 at 2PM

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate from the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institution(s).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.

K Vasantha.

MEMBER SECRETARY,
IEC, SMC, CHENNAI

MEMBER SECRETARY
ETHICAL COMMITTEE,
STANLEY MEDICAL COLLEGE
CHENNAI-600 001.

INFORMED CONSENT

GOVT. STANLEY MEDICAL COLLEGE, CHENNAI -600001

DISSERTATION TOPIC: “REGRESSION OF FIBROADENOMA IN RESPONSE TO CENTCHROMAN THERAPY, A RANDOMIZED CONTROL STUDY”.

PLACE OF STUDY: GOVT. STANLEY MEDICAL COLLEGE

I, ... have been informed about the details of the study in my own language.

I have completely understood the details of the study.

I am aware of the possible risk and benefits, while taking part in the study.

I understand that I can withdraw from the study at any point of time and even, I will continue to receive the medical treatment as usual.

I understand that I will not get any payment for taking part in the study.

I will not object if the results of this study are getting published in any medical journal, provided my personal identity is not revealed.

I know what I am supposed to do by taking part in this study and I assure that I would extend my full co-operation for this study.

Name and address of the volunteer:

Signature/Thumb impression of the volunteer

Date:

Witnesses:

(Signature , Name & Address)

Name and signature of the investigator:

DR SABARIMALI PALANISAMY

அரசு ஸ்டான்லி மருத்துவக் கல்லூரி, சென்னை - 600 001.

பங்கு பெறுபவரின் ஒப்பம்

ஆராய்ச்சியின் தலைப்பு : சாதாரண மார்பக கட்டிக்கு அறுவை சிகிச்சையில்லா மருத்துவ சிகிச்சை

ஆராய்ச்சி நடைபெறும் இடம் : அரசு ஸ்டான்லி மருத்துவக் கல்லூரி, சென்னை - 1.

பங்கு பெறுபவரின் பெயரும் முகவரியும் :

நான்,.....இந்த ஆராய்ச்சியின் விவரங்களை எனது சொந்த மொழியில் கூற அறிந்து கொண்டேன்.

இந்த ஆராய்ச்சியின் முழு விவரங்களையும் நான் அறிந்து கொண்டேன். இந்த ஆராய்ச்சியில் நான் பங்கு பெறும் போது எனக்கு ஏற்படும் நன்மை தீமைகளை முழுவதுமாக அறிந்து கொண்டேன்.

இந்த ஆராய்ச்சியின் போது எப்போது வேண்டுமானாலும் நான் விலகிக் கொள்ளலாம் என்பதயும், அதனால் எனக்கு கிடைக்கும் மருத்துவத்தில் எந்தவித மாற்றமோ பாதிப்போ இருக்காது என்றும் அறிவேன். இந்த ஆராய்ச்சியில் நான் பங்கு பெறுவதற்காக நான் எந்தவித சன்மானமும் (பணமாகவோ, பொருளாகவோ) வாங்கமாட்டேன். இந்த ஆராய்ச்சியின் முடிவுகளை, என் அடையாளங்களை குறிப்பிடாமல் மருத்துவ இதழ்களில் வெளியிட எனக்கு எந்த ஆட்சேபனையும் இல்லை. இந்த ஆரய்ச்சியில் என் பங்கு என்ன என்பதை அறிவேன். இந்த ஆராய்ச்சிக்கு எனது முழு ஒத்துழைப்பையும் தருவேன் என்று உறுதி அளிக்கிறேன்.

பங்கு பெறுபவரின் பெயரும் முகவரியும்:

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தேதி:

சாட்சி :

(சாட்சியின் பெயர், முகவரி, கையொப்பத்துடன்)

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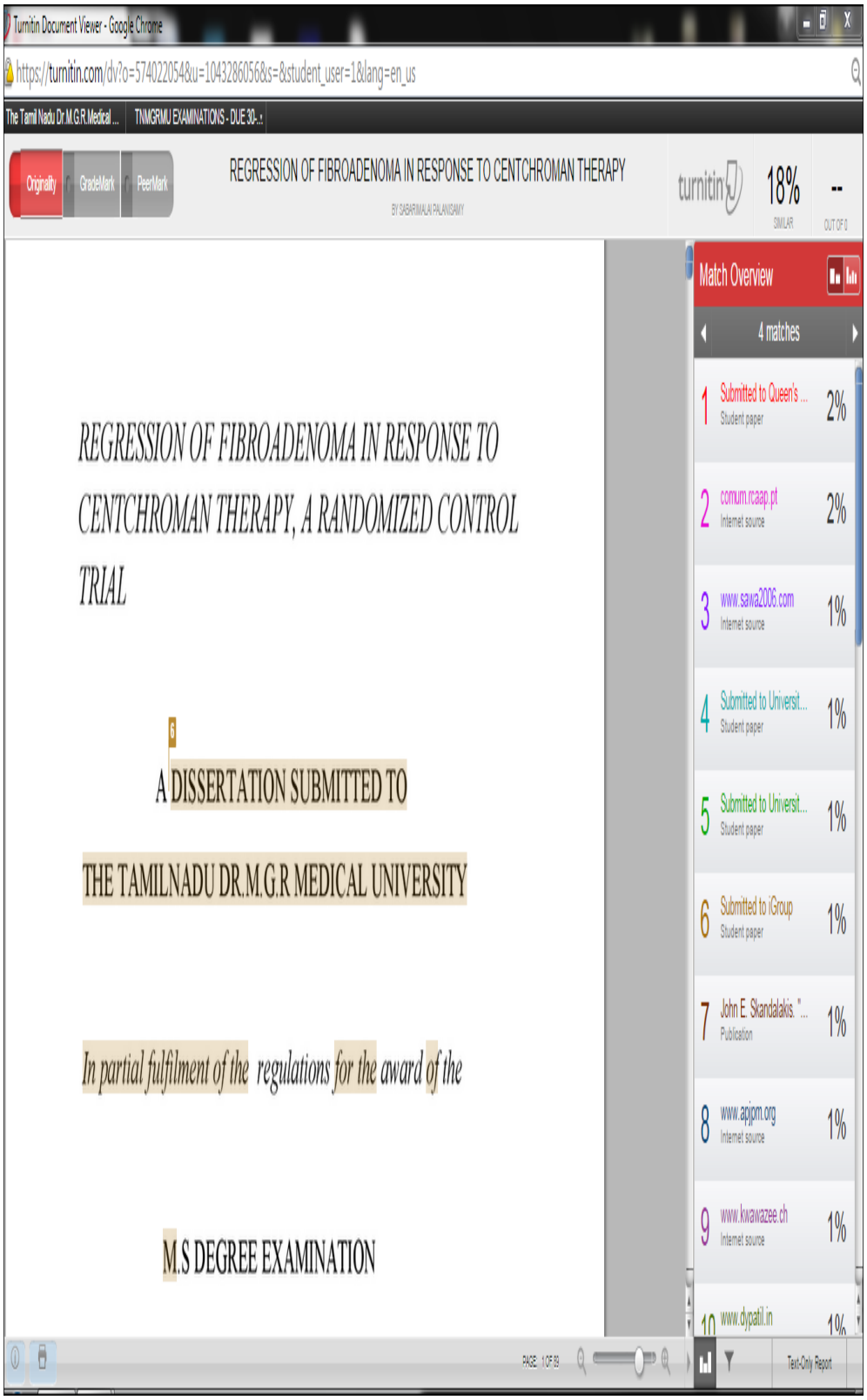
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